TITLE OF THE INVENTION

"ANGIOTENSIN II RECEPTOR BLOCKER DERIVATIVES"

******

The present invention relates to Angiotensin II Receptor Blocker (ARB) derivatives. More particularly, the present invention relates to ARB nitroderivatives, pharmaceutical compositions containing them and their use for the treatment of cardiovascular, renal and chronic liver diseases, inflammatory processes and metabolic syndromes.

With the angiotensin II receptor blockers a class of compounds is intended, comprising as main components Losartan, EXP3174, Candesartan, Telmisartan, Valsartan, Eprosartan, Irbesartan and Olmesartan.

ARBs are approved only for the treatment of hypertension, the antihypertensive activity is due mainly to selective blockade of AT_1 receptors and the consequent reduced pressor effect of angiotensin II. Angiotensin II stimulates the synthesis and secretion of aldosterone and raises blood pressure via a potent direct vasoconstrictor effect.

Now, it has been reported that angiotensin II receptor blockers have side-effects such as for example hypotension, hyperkalaemia, myalgia, respiratory-tract disorders, renal disorders, back pain, gastrointestinal disturbances, fatigue, and neutropenia (Martindale, Thirty-third edition, p. 921).

It was now object of the present invention to provide new derivatives of ARBs able not only to eliminate or at least reduce the side effects associated with their parent compounds, but also having an improved pharmacological activity. It has been so surprisingly found that angiotensin II receptor blocker nitroderivatives have a

significantly improved overall profile as compared to native compounds both in term of wider pharmacological activity and enhanced tolerability.

In particular, it has been recognized that the angiotensin II receptor blocker nitroderivatives of the present invention exhibit a strong anti-inflammatory, antithrombotic and antiplatelet activity and can be furthermore employed for treating or preventing heart failure, myocardial infarction, ischemic stroke, atherosclerosis, ocular and pulmonary hypertension, hypertension, diabetic nephropathy, peripheral vascular diseases, left ventricular dysfunction and hypertrophy, liver fibrosis, portal hypertension and metabolic syndromes.

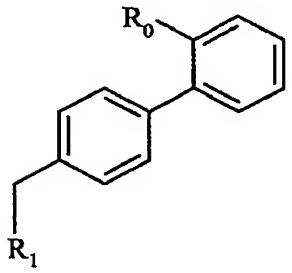
Object of the present invention are, therefore, Angiotensin II Receptor Blocker nitroderivatives of general formula (I) and pharmaceutically acceptable salts or stereoisomers thereof:

$$R-(Y-ONO_2)_s \quad (I)$$

wherein:

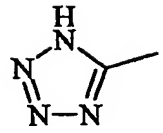
s is an integer equal to 1 or 2;

R is selected from the following Angiotensin II Receptor Blocker residues of formula (II) or (III):



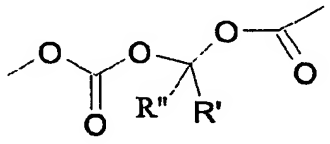
(II)

wherein:

R_0 is 

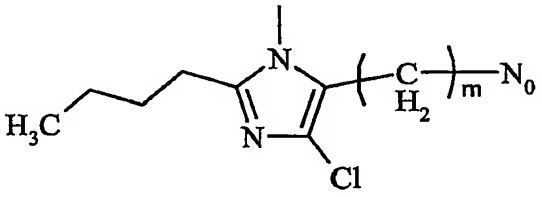
or $-N_0$ which is a group capable to bind to Y, having one of the following meaning:

-COO-, -O-, -CONH-, -OCO-, -OCOO- or

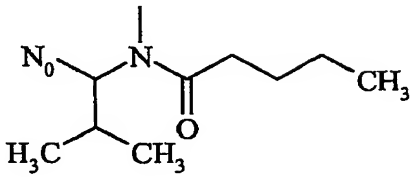


wherein R' and R'' are the same or different, and are H or straight or branched C_1-C_4 alkyl;

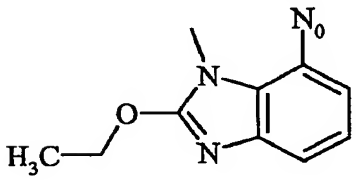
R_1 is selected from the group consisting of:



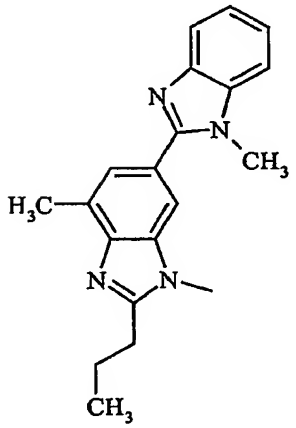
(IIa)



(IIb)

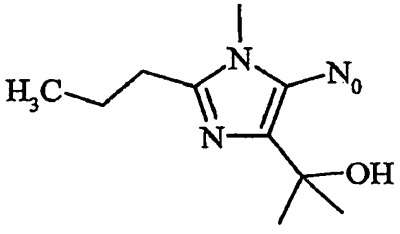


(IIc)



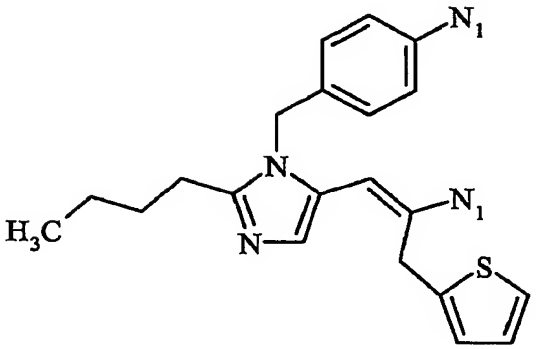
(IId)

or



(IIe)

wherein m is an integer equal to 0 or 1 and N_0 is as above defined;



(III)

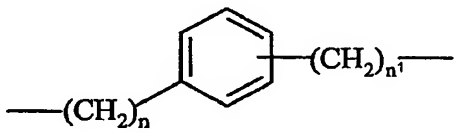
wherein N_1 has the same meaning as N_0 or is equal to -COOH; with the proviso that at least one of the groups N_1 is equal to -COO- or -CONH-, i.e. it is a group capable to bind to Y;

Y is a bivalent radical having the following meaning:

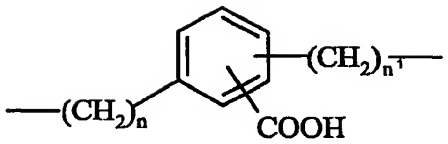
a)

- straight or branched C_1-C_{20} alkylene, preferably C_1-C_{10}, being optionally substituted with one or more of the substituents selected from the group consisting of: halogen atoms, hydroxy, $-ONO_2$ or T_0, wherein T_0 is $-OC(O)(C_1-C_{10}$ alkyl$)-ONO_2$ or $-O(C_1-C_{10}$ alkyl$)-ONO_2$;
- cycloalkylene with 5 to 7 carbon atoms into cycloalkylene ring, the ring being optionally substituted with side chains T, wherein T is straight or branched alkyl with from 1 to 10 carbon atoms, preferably CH_3;

b)

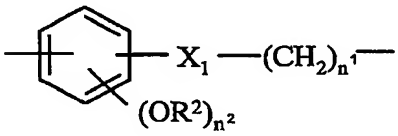


c)



wherein n is an integer from 0 to 20, and n^1 is an integer from 1 to 20;

d)

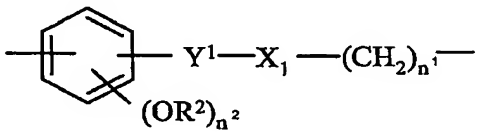


wherein:

n^1 is as defined above and n^2 is an integer from 0 to 2;

X_1 = -OCO- or -COO- and R^2 is H or CH_3;

e)

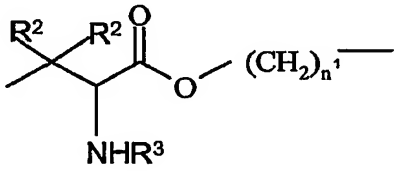


wherein:

n^1, n^2, R^2 and X_1 are as defined above;

Y^1 is $-CH_2-CH_2-$ or $-CH=CH-(CH_2)_{n^2}-$;

f)

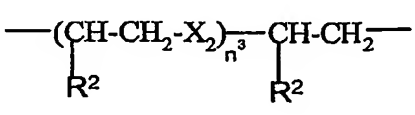


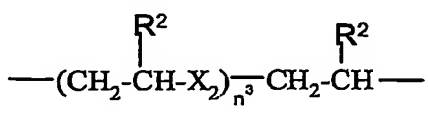
wherein:

n^1 and R^2 are as defined above, R^3 is H or $-COCH_3$;

with the proviso that when Y is selected from the bivalent radicals mentioned under b)-f), the $-ONO_2$ group is linked to a $-(CH_2)_{n^1}$ group;

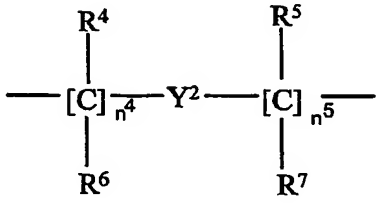
g)





wherein X_2 is -O- or -S-, n^3 is an integer from 1 to 6, preferably from 1 to 4, R^2 is as defined above;

h)



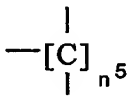
wherein:

n^4 is an integer from 0 to 10;

n^5 is an integer from 1 to 10;

R^4, R^5, R^6, R^7 are the same or different, and are H or straight or branched C_1-C_4 alkyl, preferably R^4, R^5, R^6, R^7 are H;

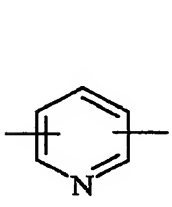
wherein the $-ONO_2$ group is linked to



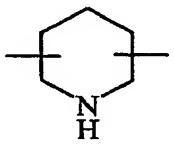
wherein n^5 is as defined above;

Y^2 is an heterocyclic saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulfur,

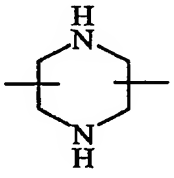
and is selected from



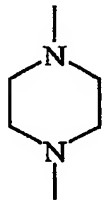
(Y1)



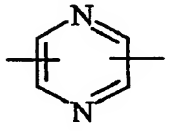
(Y2)



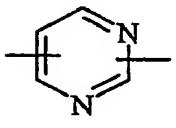
(Y3)



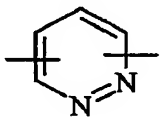
(Y4)



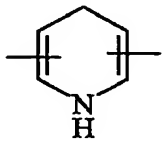
(Y5)



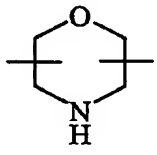
(Y6)



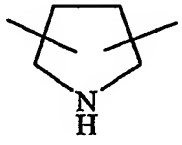
(Y7)



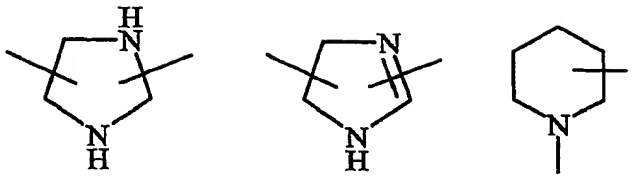
(Y8)



(Y9)



(Y10)



(Y11) (Y12) (Y13)

The term "C_1-C_{20} alkylene" as used herein refers to branched or straight chain C_1-C_{20} hydrocarbon, preferably having from 1 to 10 carbon atoms such as methylene, ethylene, propylene, isopropylene, n-butylene, pentylene, n-hexylene and the like.

The term "C_1-C_{10} alkyl" as used herein refers to branched or straight chain alkyl groups comprising one to ten carbon atoms, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, hexyl, octyl and the like.

The term "cycloalkylene" as used herein refers to ring having from 5 to 7 carbon atoms including, but not limited to, cyclopentylene, cyclohexylene optionally substituted with side chains such as straight or branched (C_1-C_{10})-alkyl, preferably CH_3.

The term "heterocyclic" as used herein refers to saturated, unsaturated or aromatic 5 or 6 members ring, containing one or more heteroatoms selected from nitrogen, oxygen, sulphur, such as for example pyridine, pyrazine, pyrimidine, pyrrolidine, morpholine, imidazole and the like.

Another aspect of the present invention provides the use of the compounds of formula (I) in combination with at least a compound used to treat cardiovascular disease selected from the group consisting of: ACE inhibitors, HMGCoA reductase inhibitors, beta-adrenergic blockers, calcium channel blockers, diuretics, antithrombotics such

as aspirin, nitrosated ACE inhibitors, nitrosated HMGCoA reductase inhibitors, nitrosated beta-adrenergic blockers, nitrosated aspirin and nitrosated diuretics.

Suitable ACE inhibitors, HMGCoA reductase inhibitors, beta-adrenergic blockers, calcium channel blockers, antithrombotics and diuretics are described in the literature such as The Merck Index (13^{th} edition).

Suitable nitrosated compounds are disclosed in WO 98/21193, WO 97/16405 and WO 98/09948.

The administration of the compounds above reported can be carried out simultaneously or successively.

The present invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the compounds and/or compositions of the present invention and one or more of the compounds used to treat cardiovascular diseases reported above.

As stated above, the invention includes also the pharmaceutically acceptable salts of the compounds of formula (I) and stereoisomers thereof.

Examples of pharmaceutically acceptable salts are either those with inorganic bases, such as sodium, potassium, calcium and aluminium hydroxides, or with organic bases, such as lysine, arginine, triethylamine, dibenzylamine, piperidine and other acceptable organic amines.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in an organic solvent such as acetonitrile, tetrahydrofuran with the corresponding organic or inorganic acids.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acids. Examples of inorganic acids

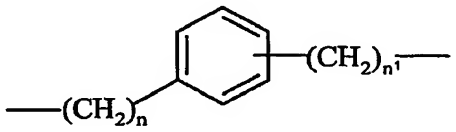
are: nitric, hydrochloric, sulphuric, phosphoric acids. Salts with nitric acid are preferred.

The compounds of the invention which have one or more asymmetric carbon atoms can exist as optically pure enantiomers, pure diastereomers, enantiomers mixtures, diastereomers mixtures, enantiomer racemic mixtures, racemates or racemate mixtures. Within the object of the invention are also all the possible isomers, stereoisomers and their mixtures of the compounds of formula (I).

Preferred compounds are those of formula (I) wherein:
s and R are as above defined;
Y is a bivalent radical having the following meaning:
a)

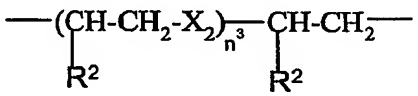
- straight or branched C_1-C_{10} alkylene, being optionally substituted with T_0, wherein T_0 is as above defined;

b)



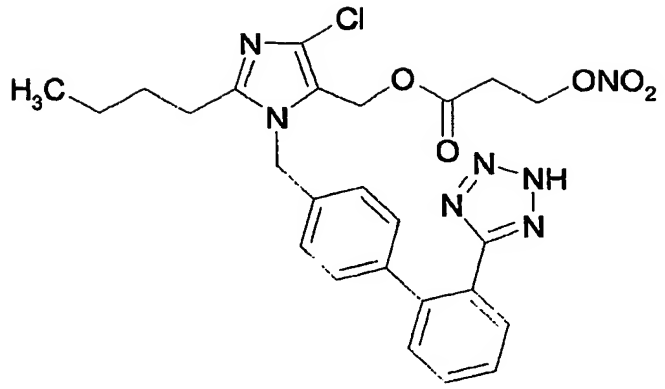
wherein n is an integer equal to 0 or 1, and n^1 is an integer equal to 1; with the proviso the $-ONO_2$ group is linked to a $-(CH_2)_{n^1}$ group;

g)

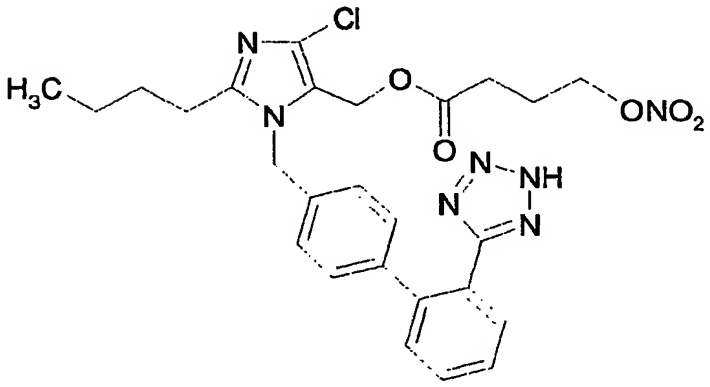


wherein X_2 is -O- or -S-, n^3 is an integer equal to 1 and R^2 is H;

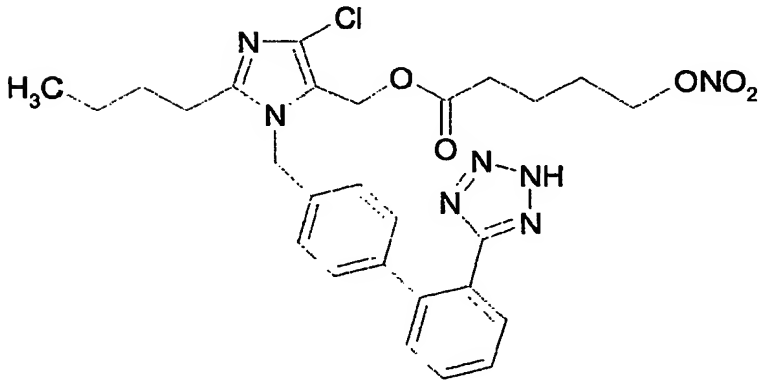
The following are preferred compounds according to the present invention:



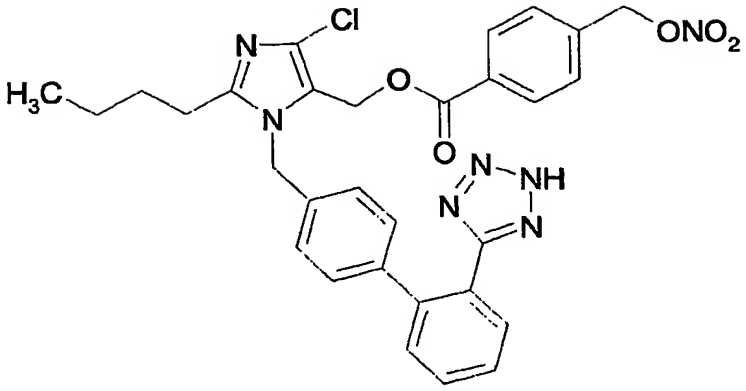
(1)



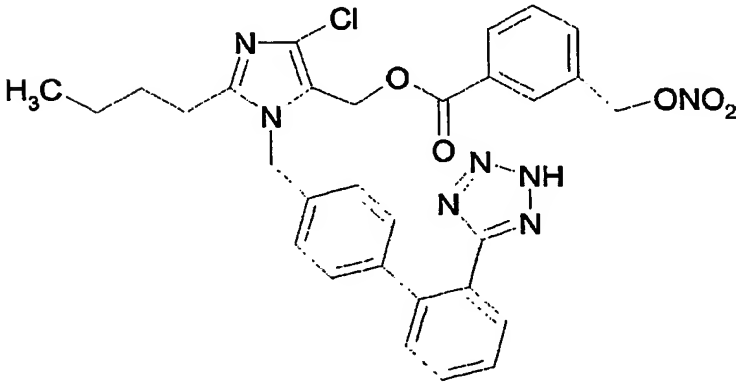
(2)



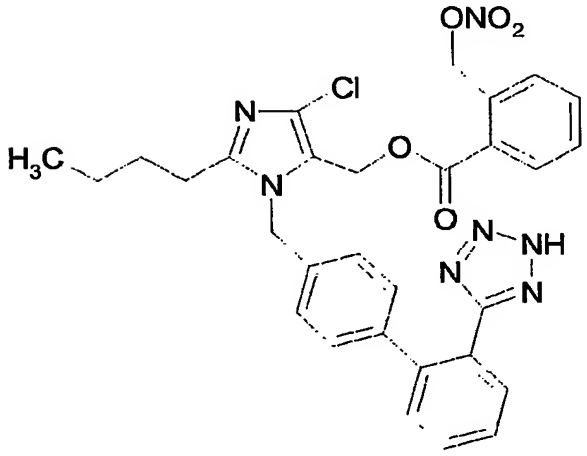
(3)



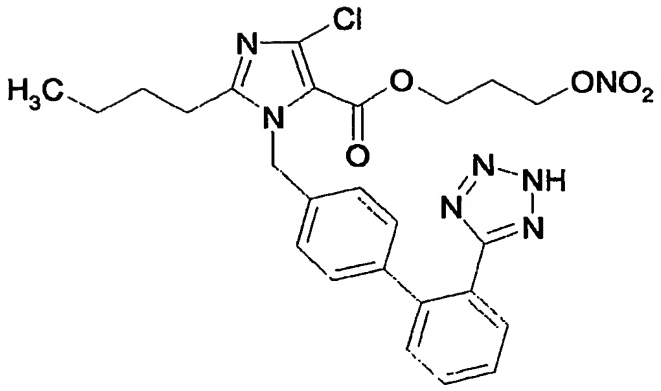
(4)



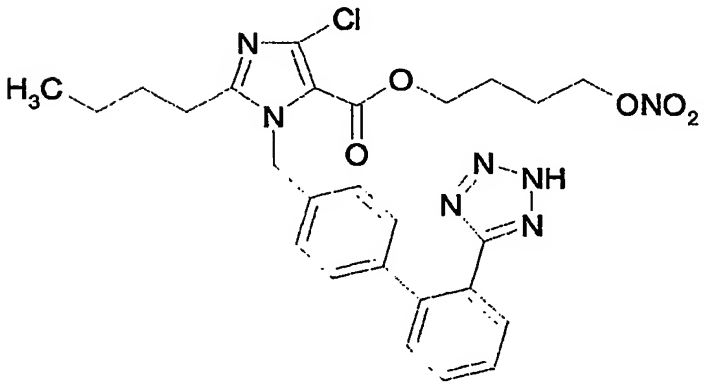
(5)



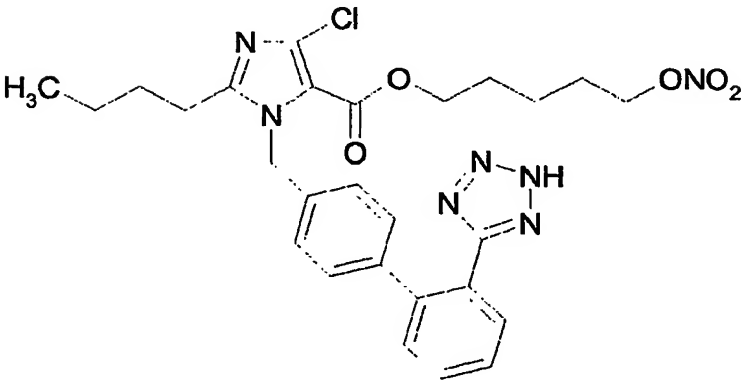
(6)



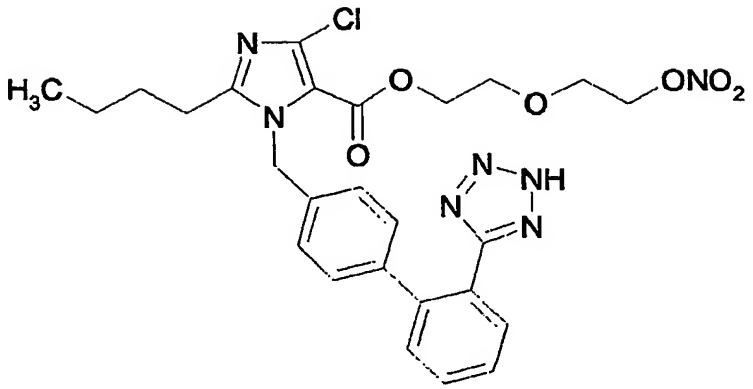
(7)



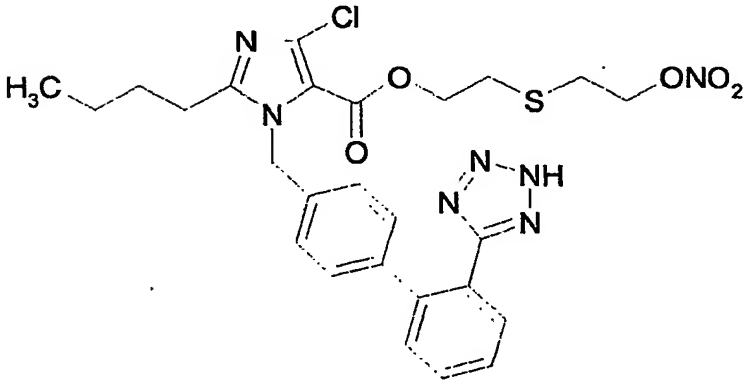
(8)



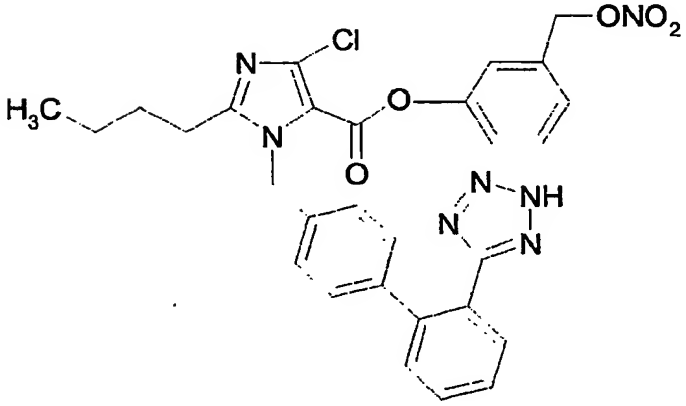
(9)



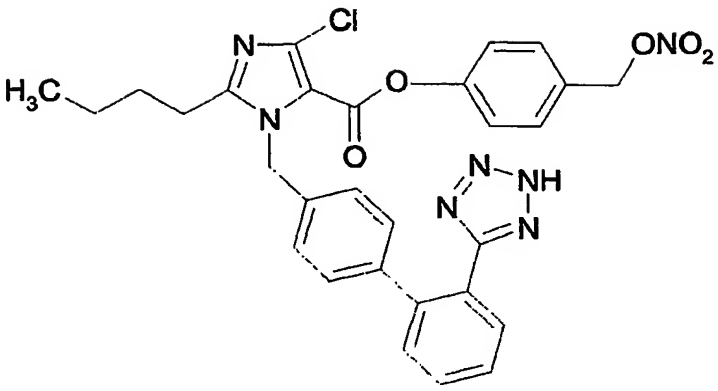
(10)



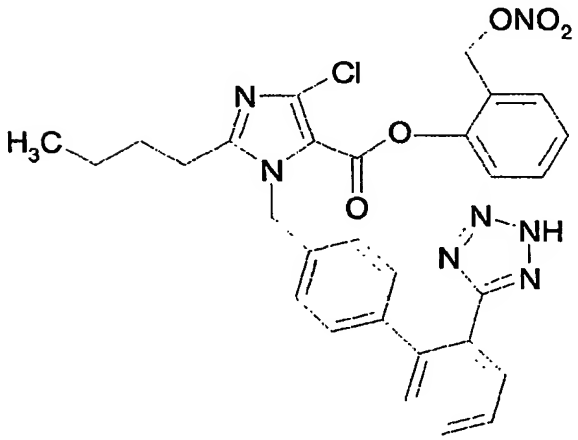
(11)



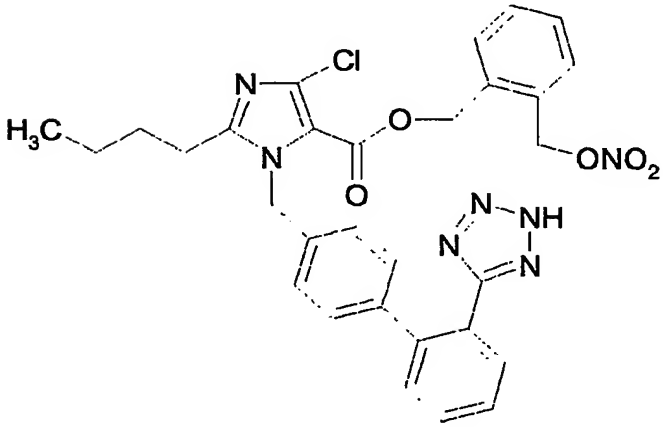
(12)



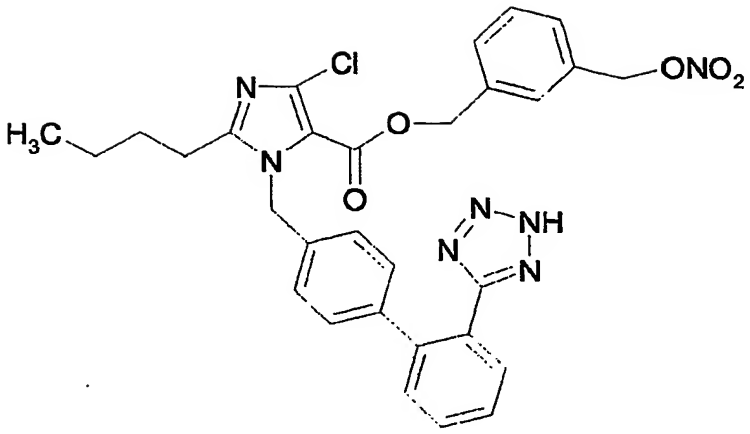
(13)



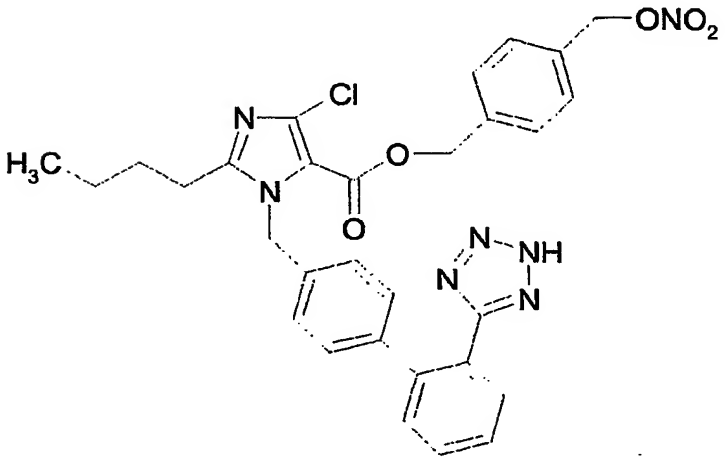
(14)



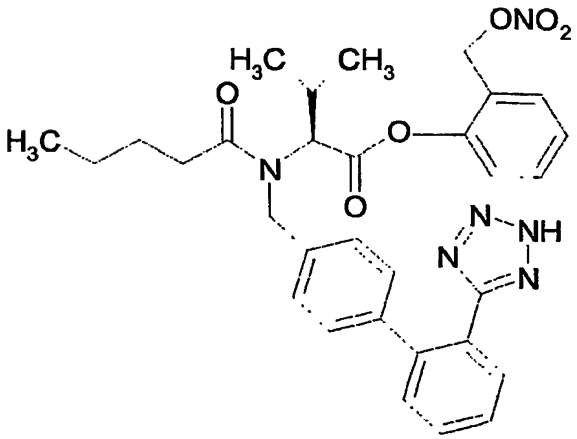
(15)



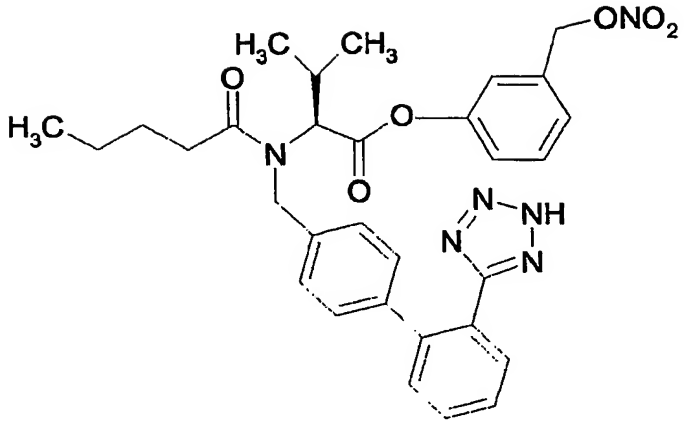
(16)



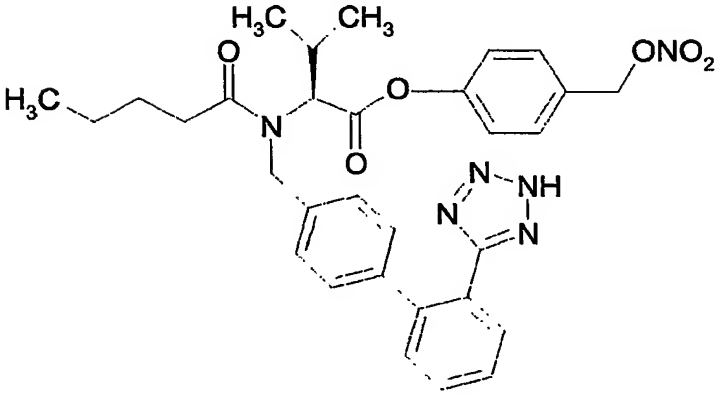
(17)



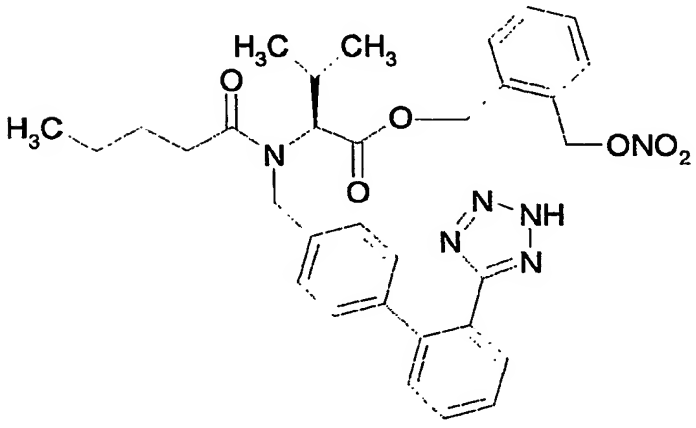
(18)



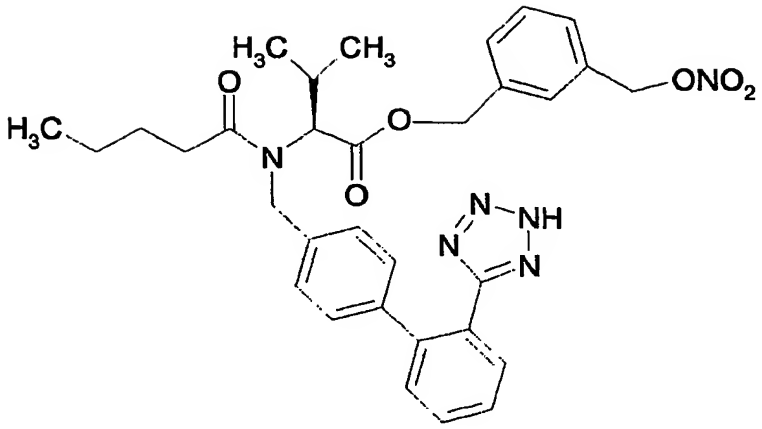
(19)



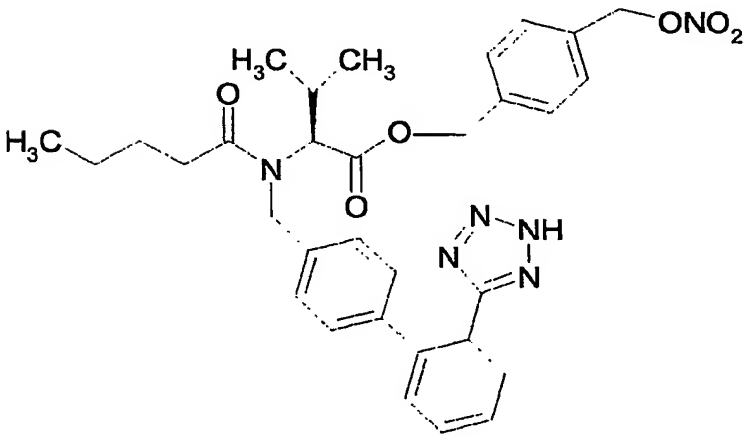
(20)



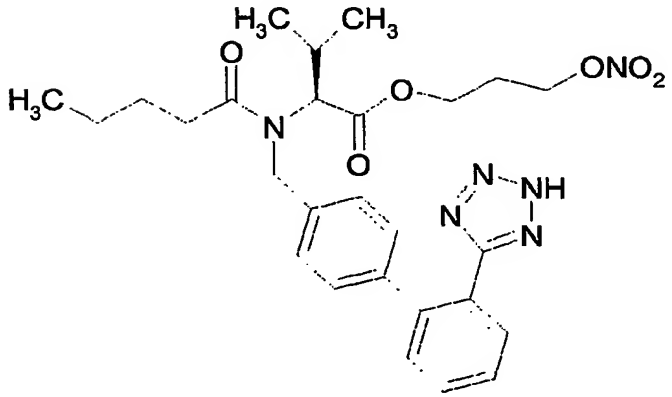
(21)



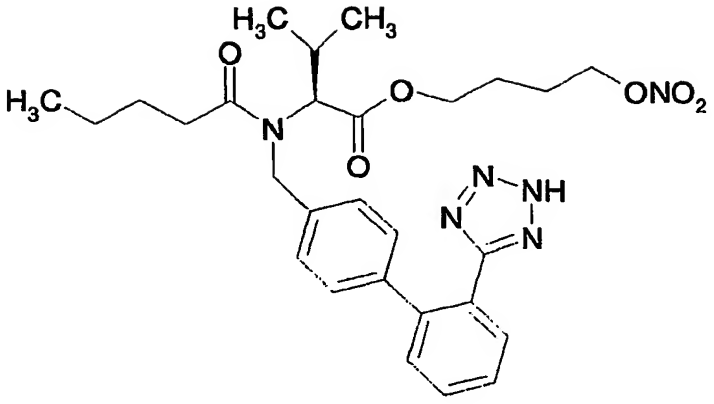
(22)



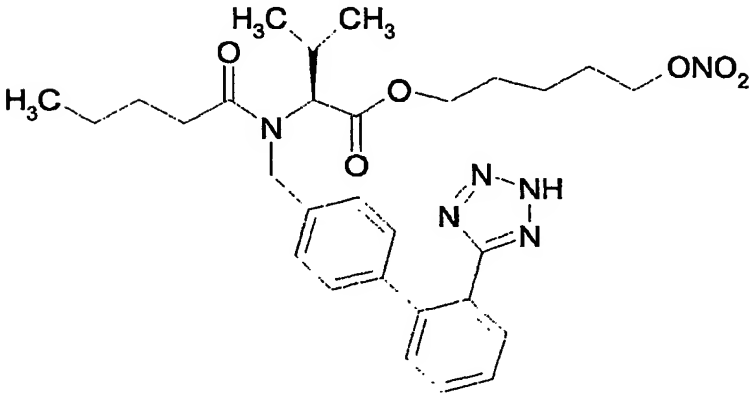
(23)



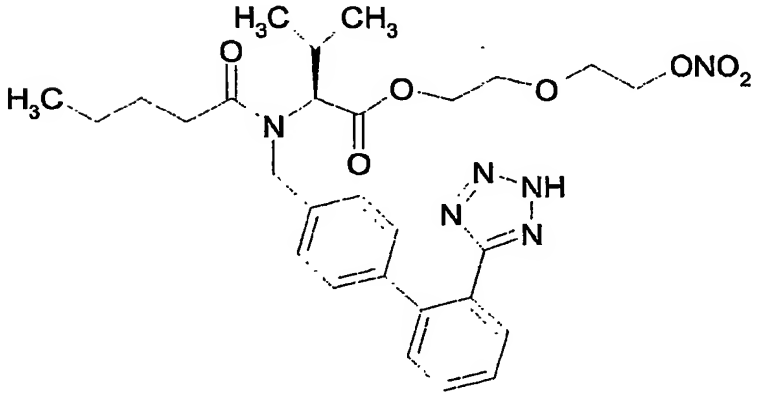
(24)



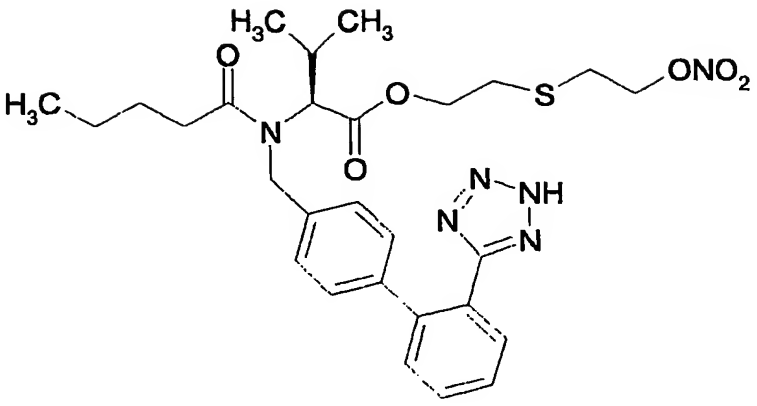
(25)



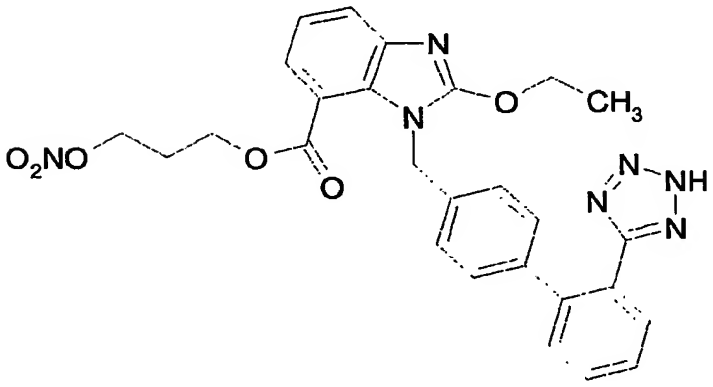
(26)



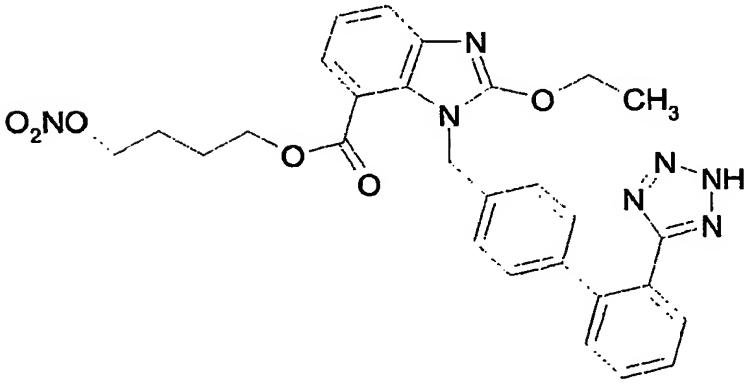
(27)



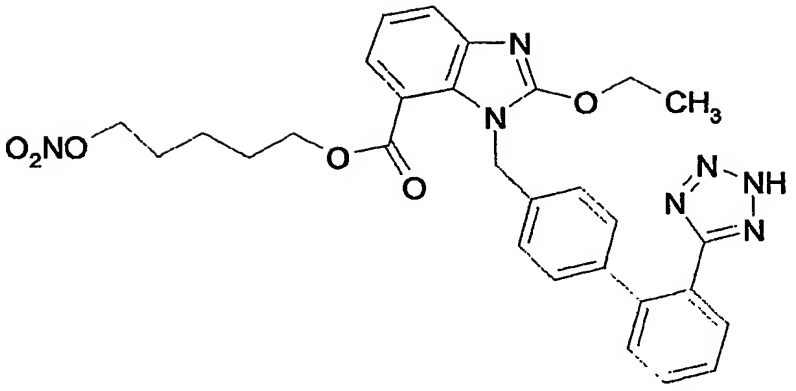
(28)



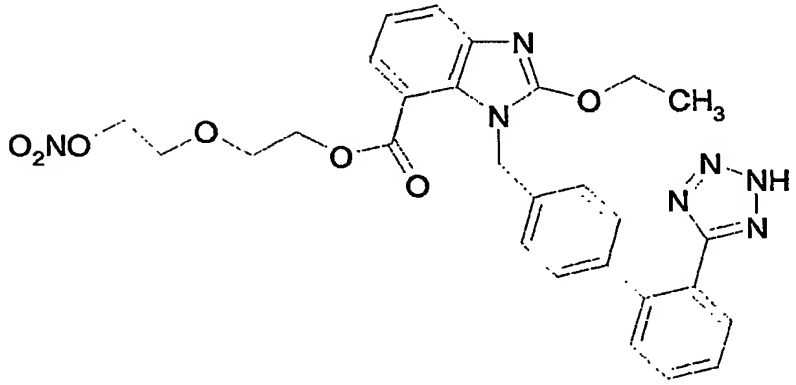
(29)



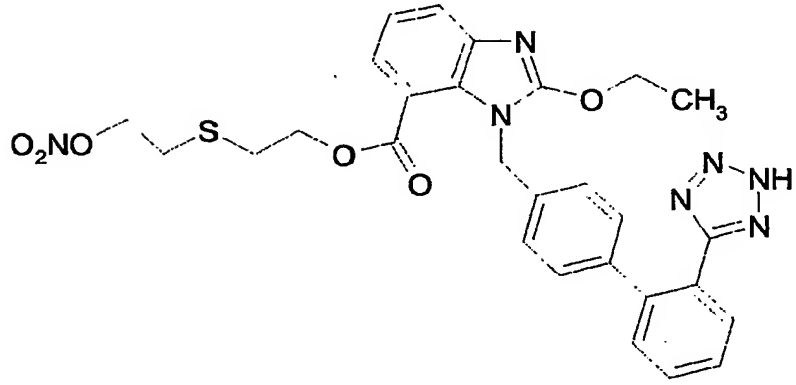
(30)



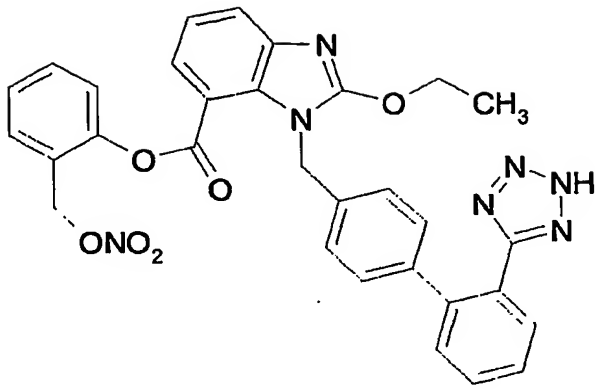
(31)



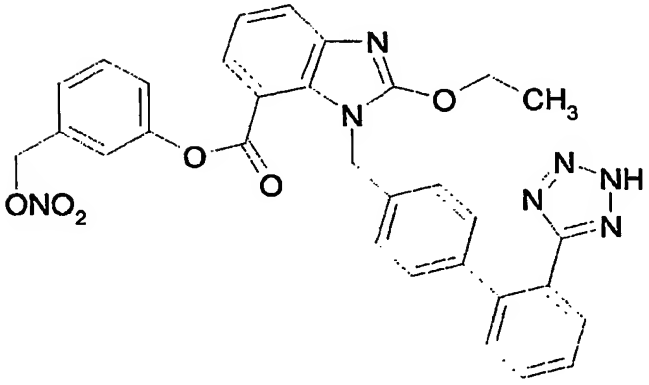
(32)



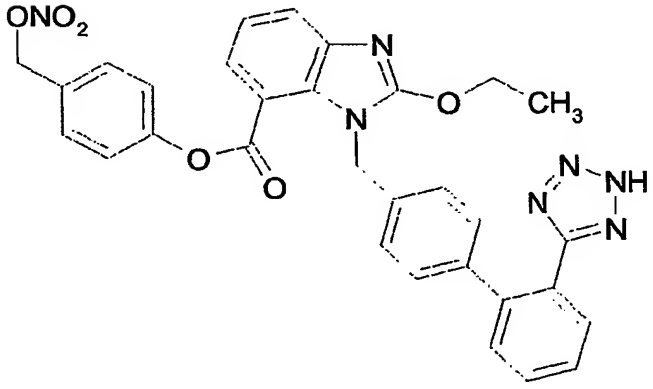
(33)



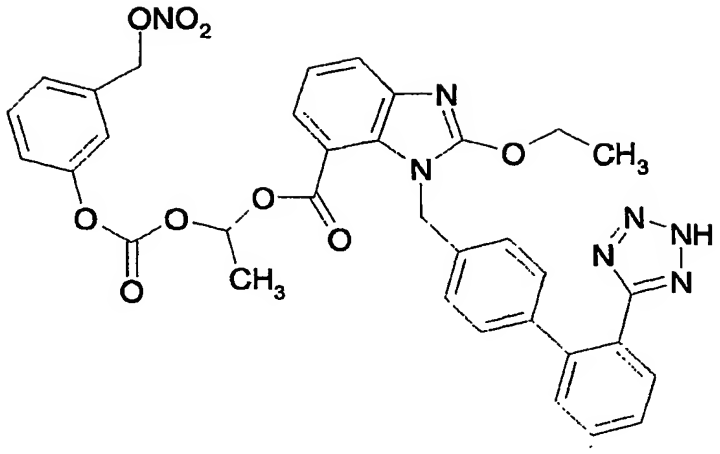
(34)



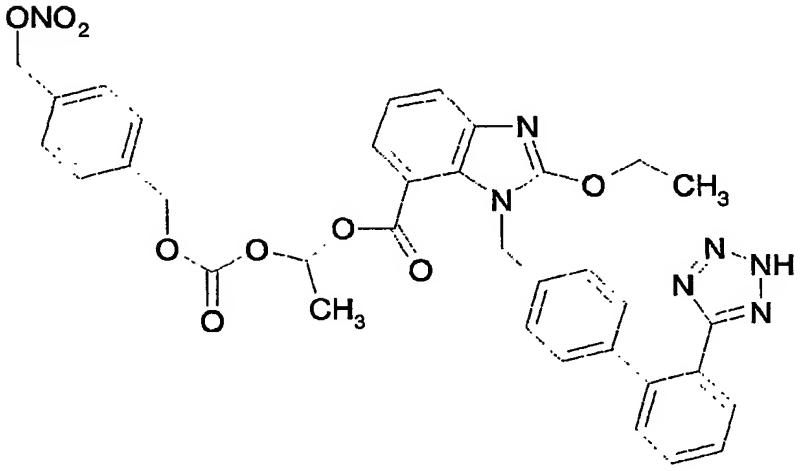
(35)



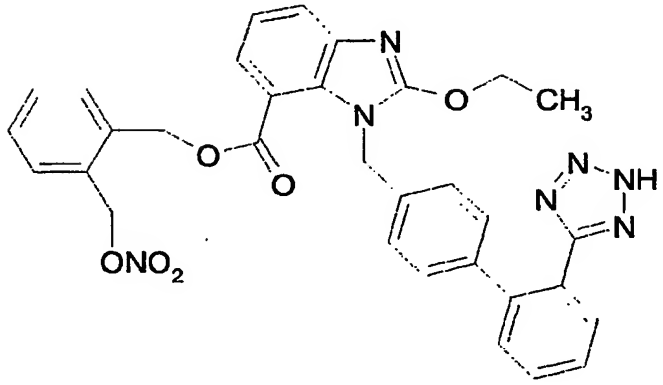
(36)



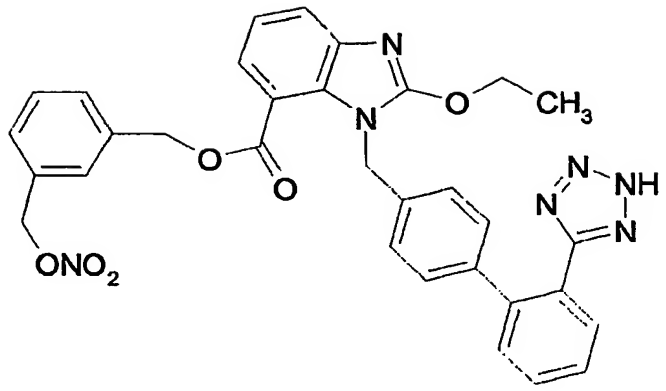
(37)



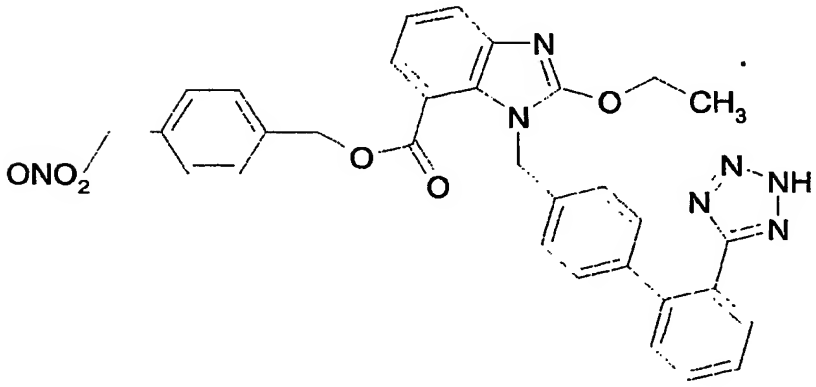
(38)



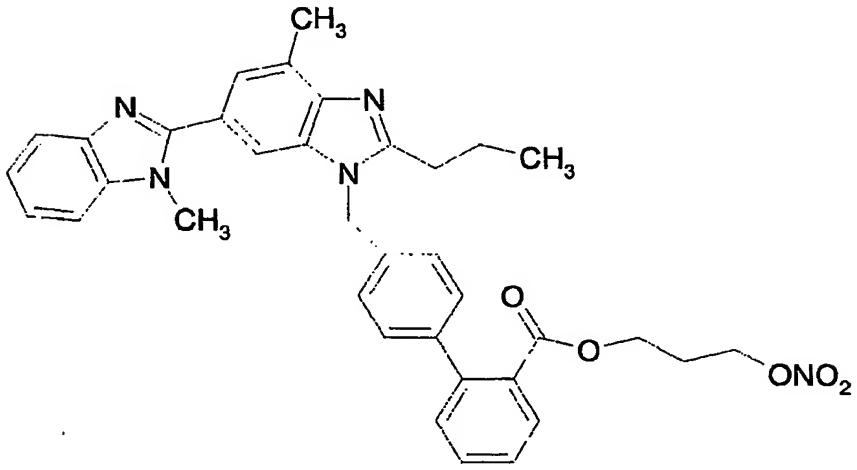
(39)



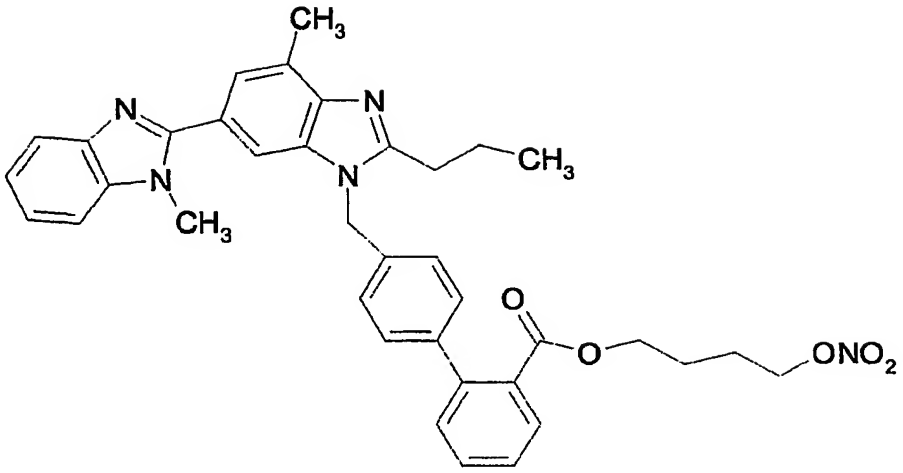
(40)



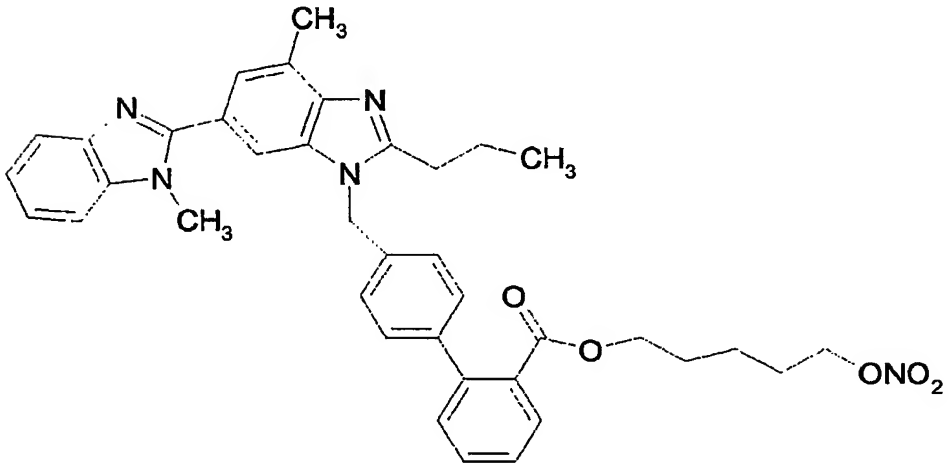
(41)



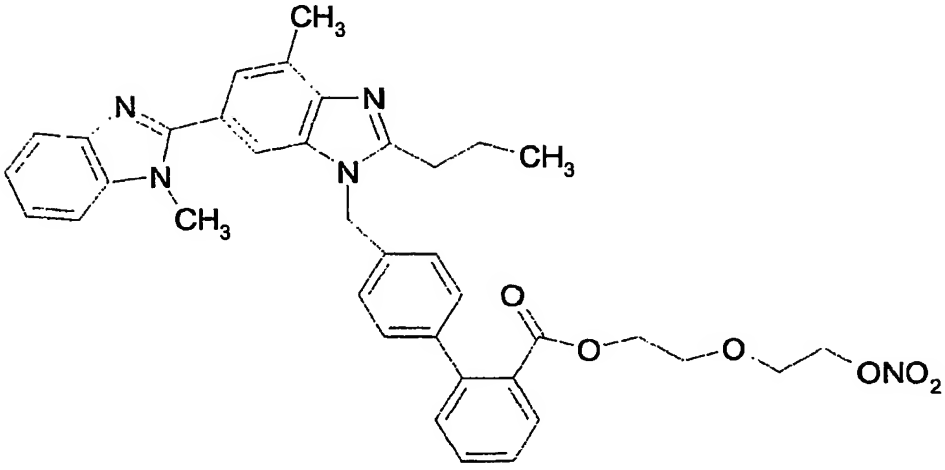
(42)



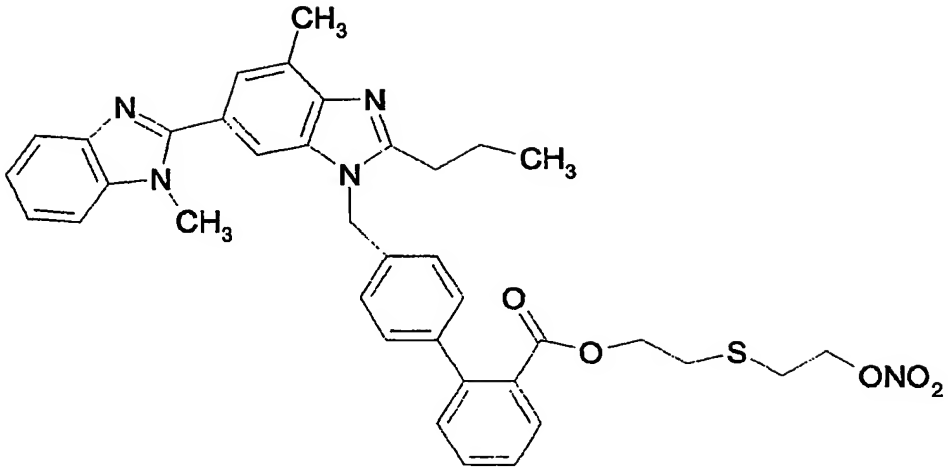
(43)



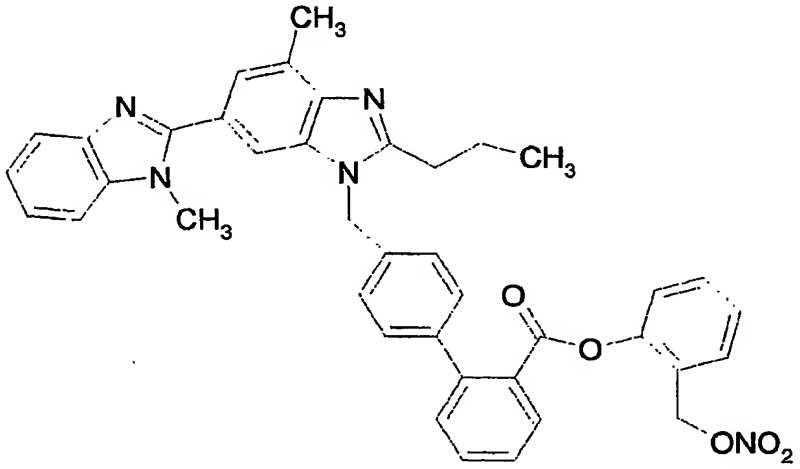
(44)



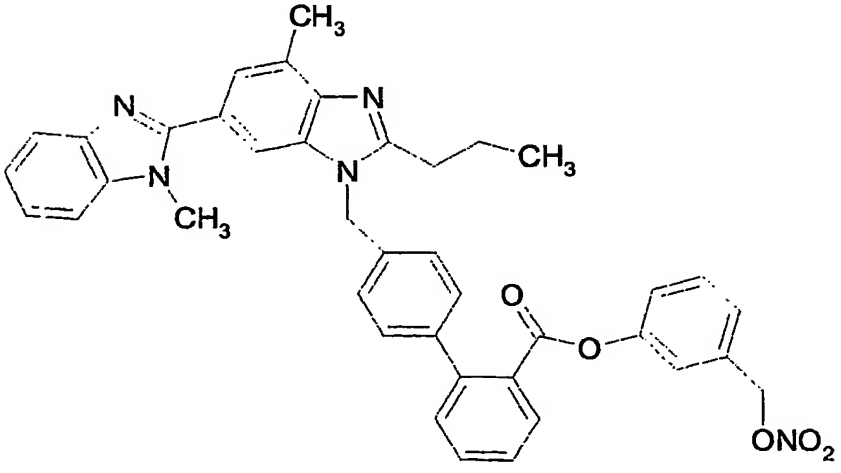
(45)



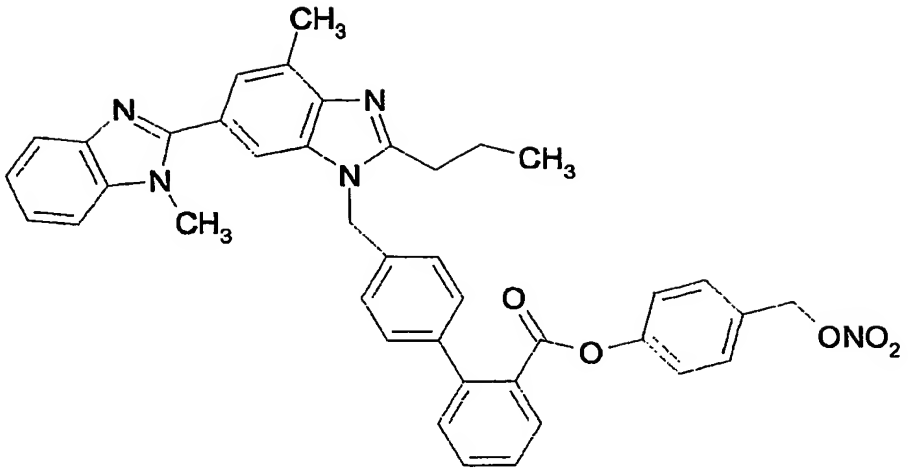
(46)



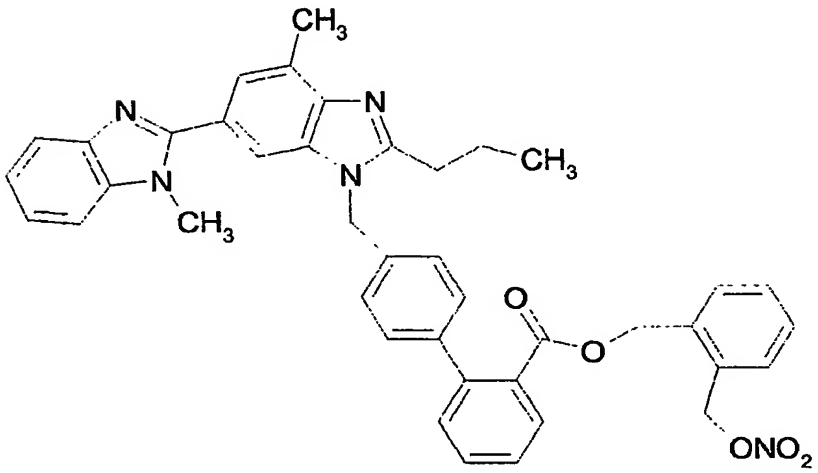
(47)



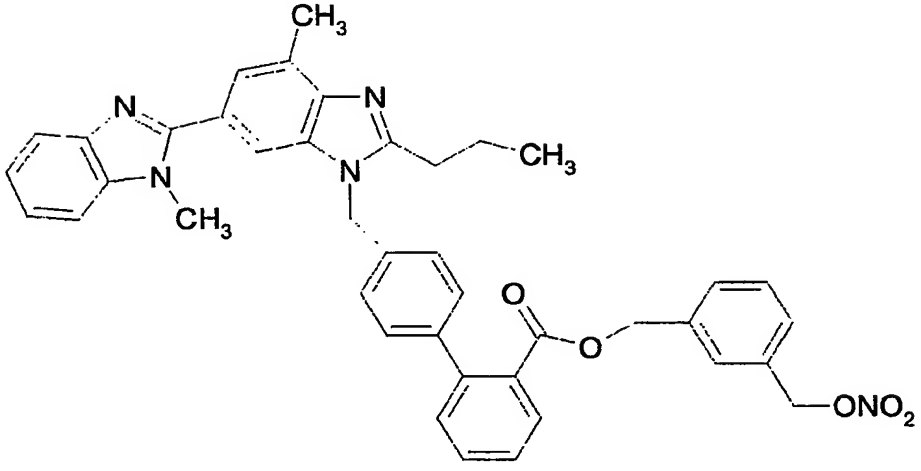
(48)



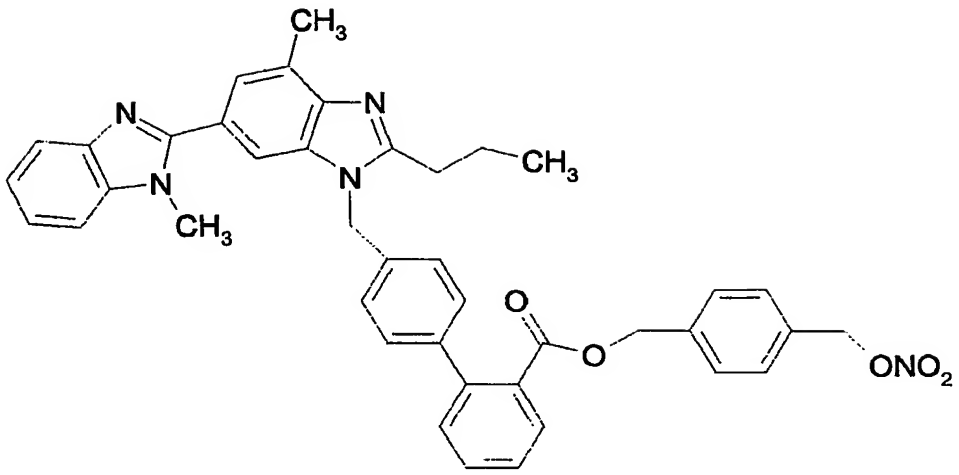
(49)



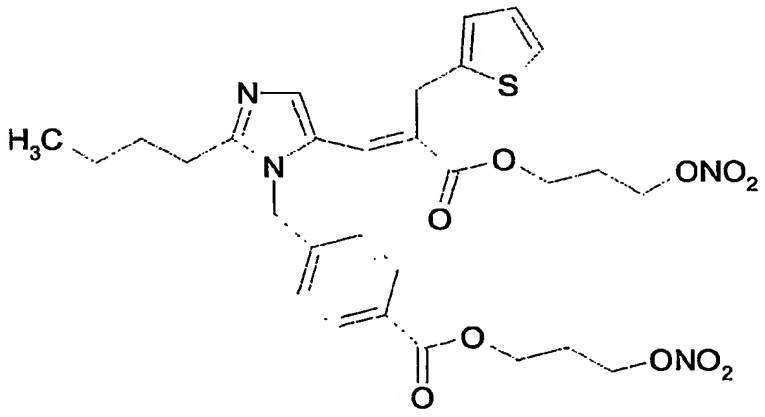
(50)



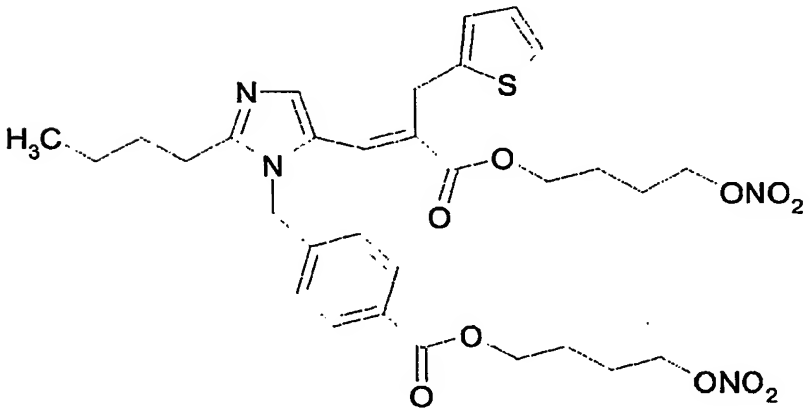
(51)



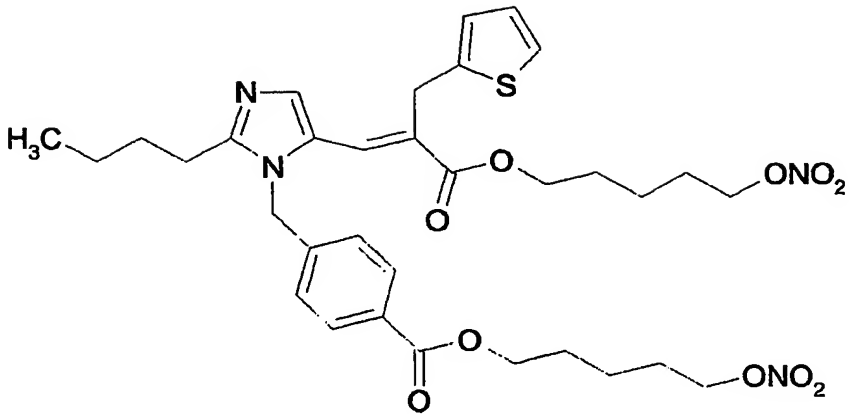
(52)



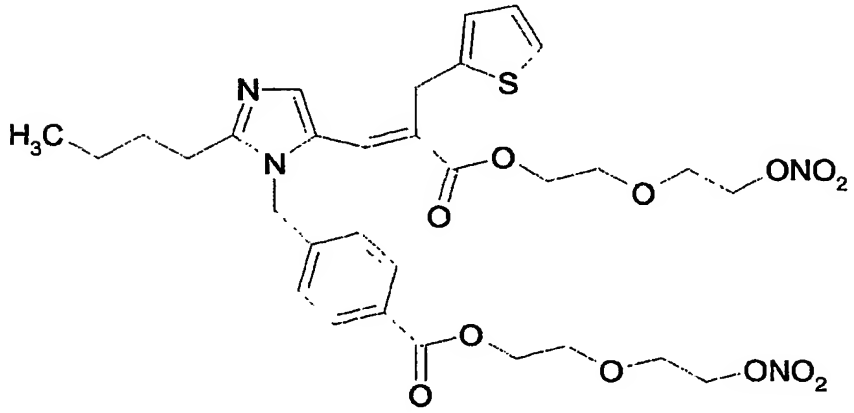
(53)



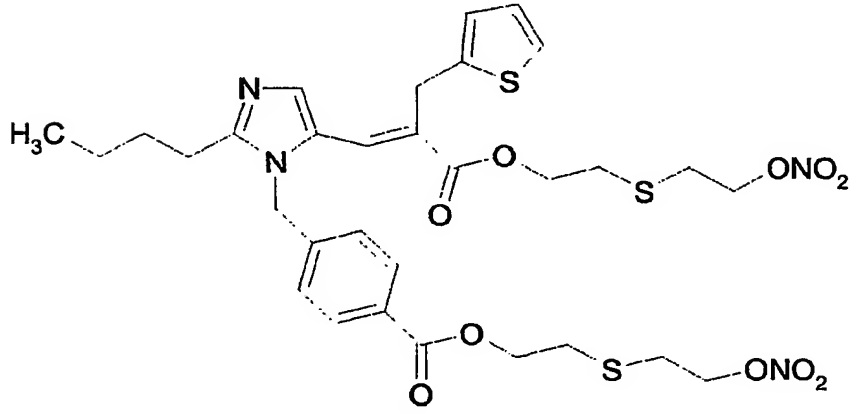
(54)



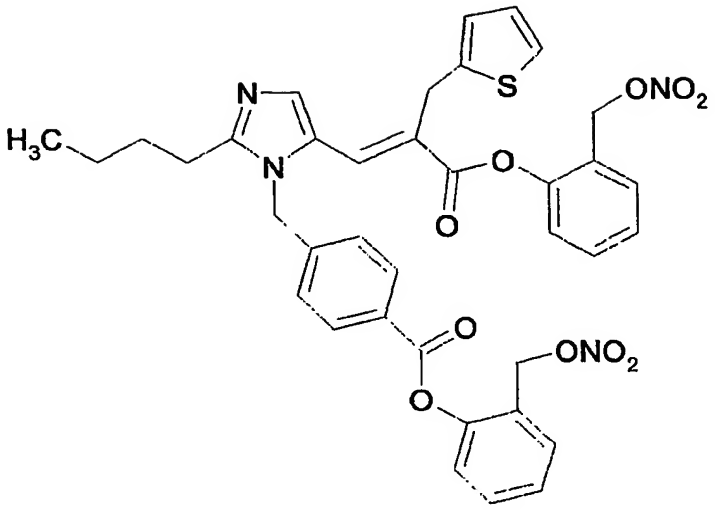
(55)



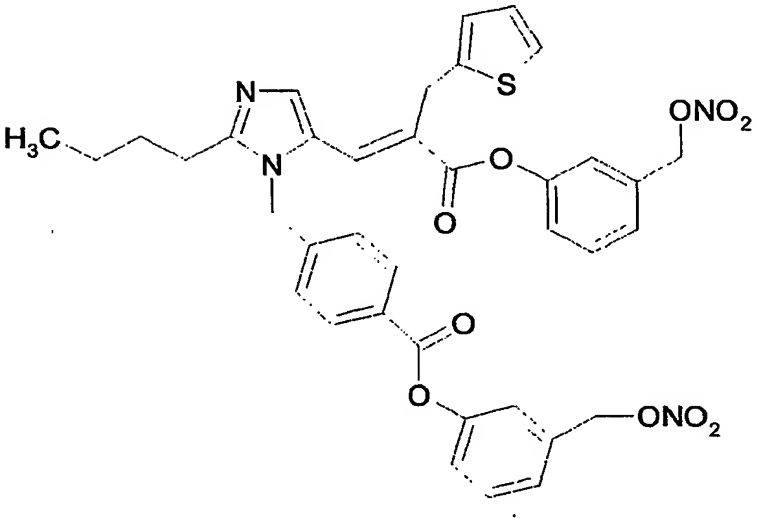
(56)



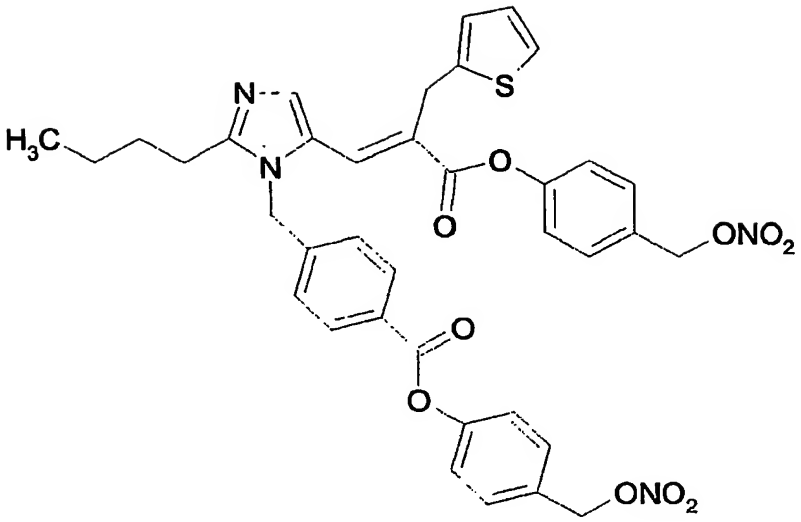
(57)



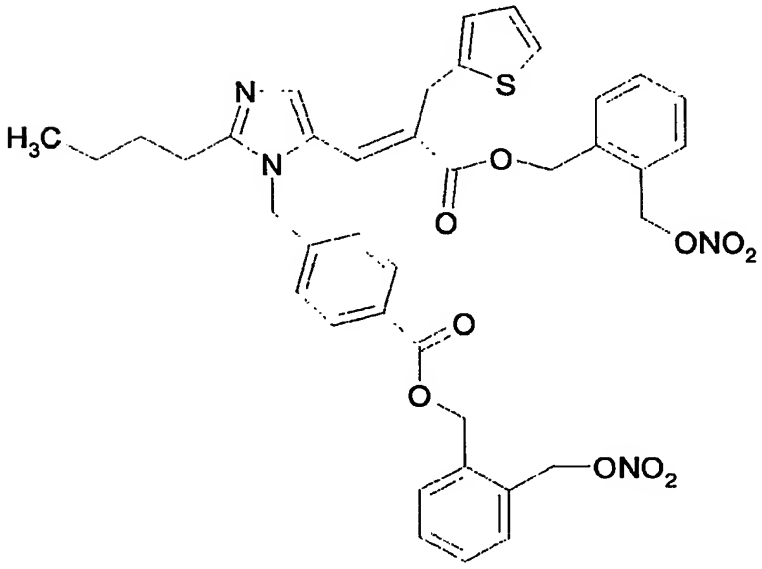
(58)



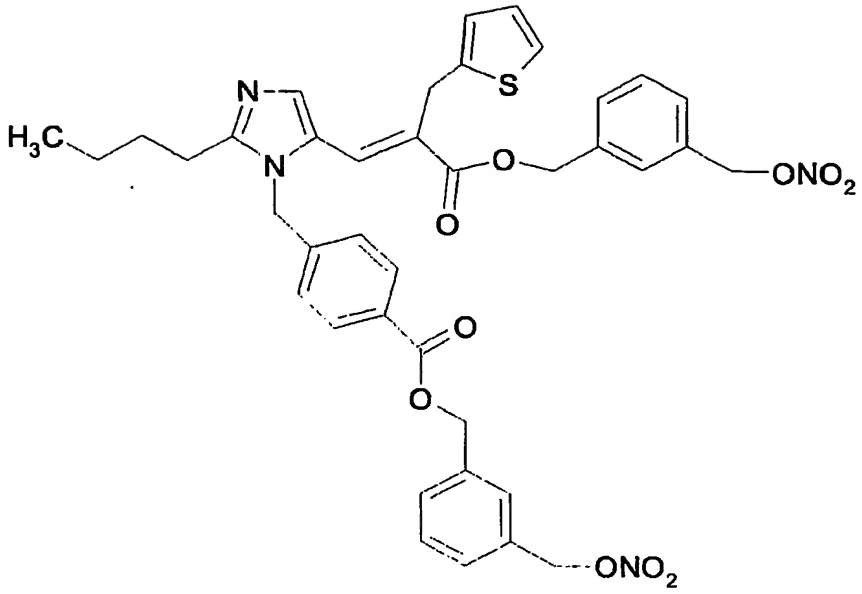
(59)



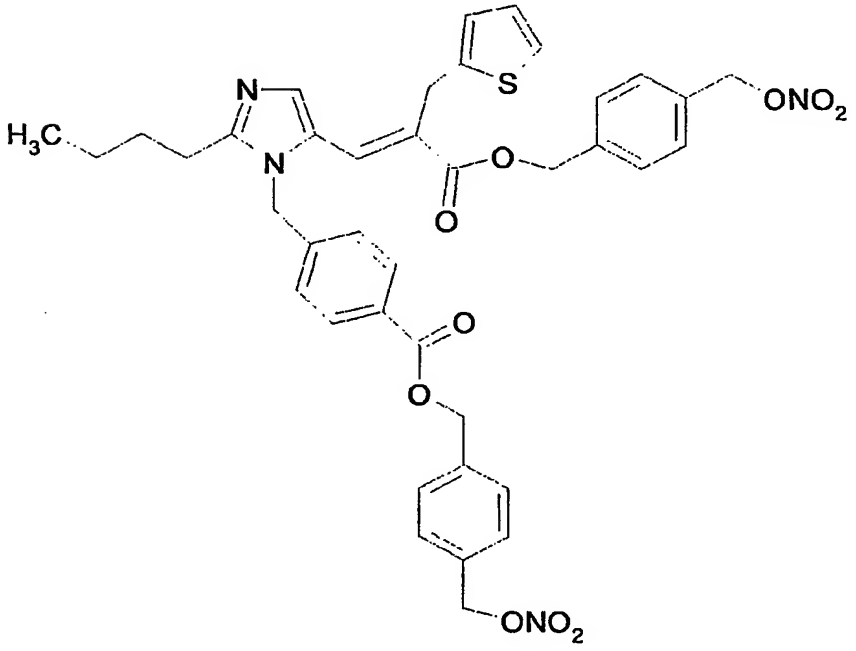
(60)



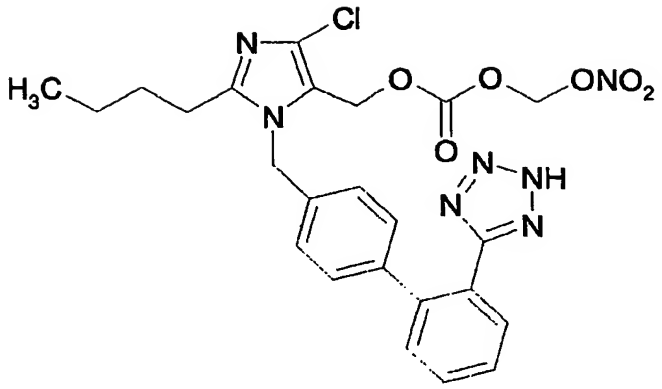
(61)



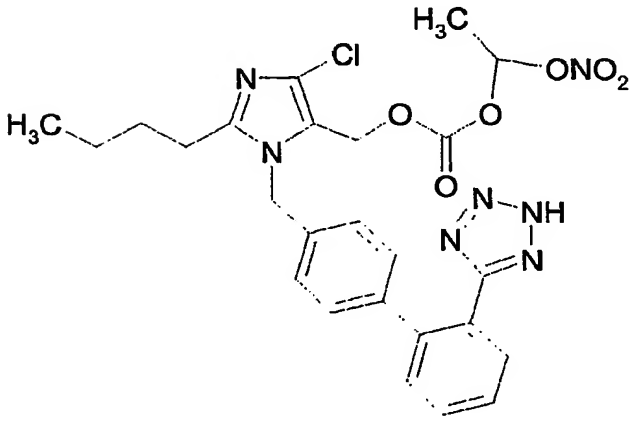
(62)



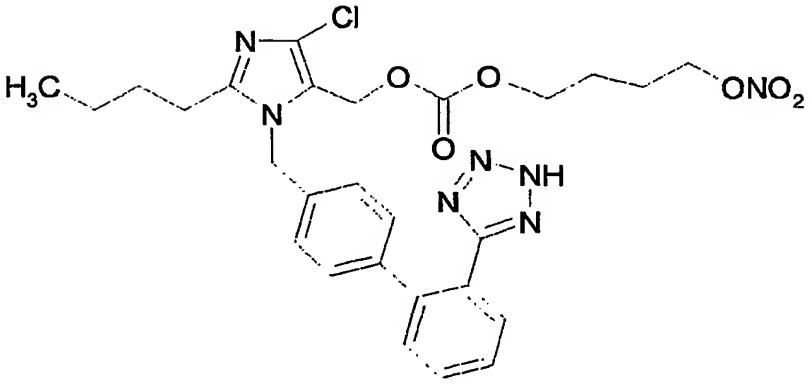
(63)



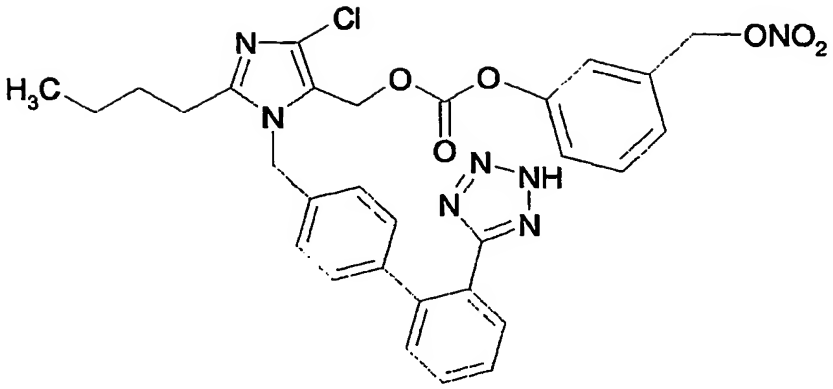
(64)



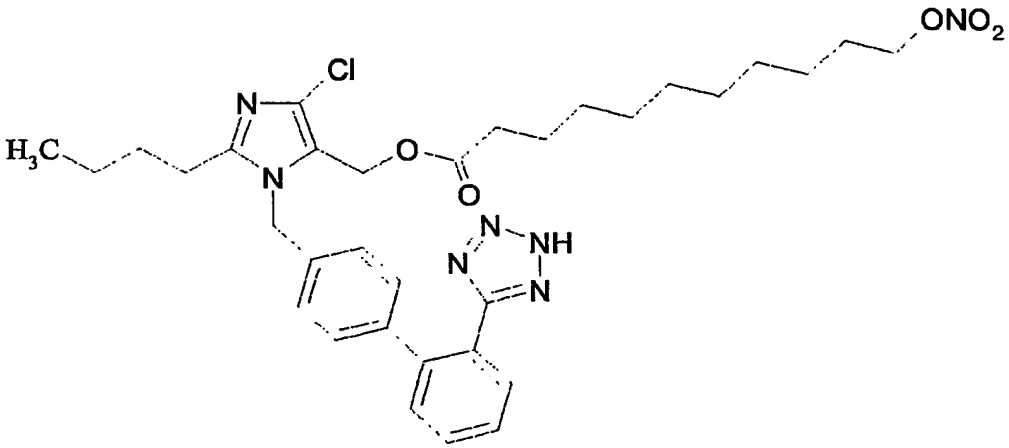
(65)



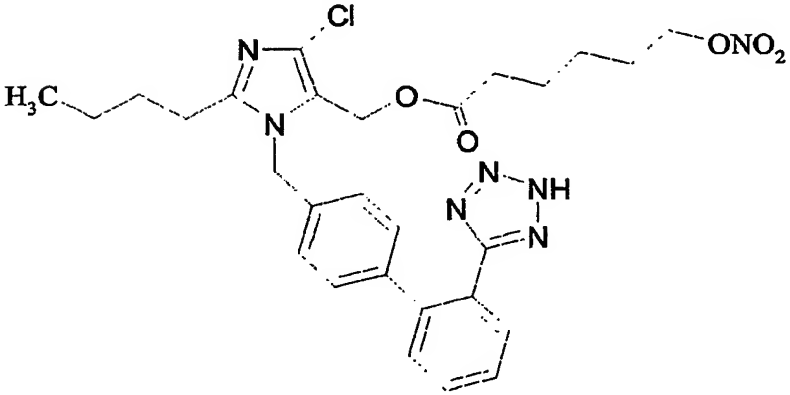
(66)



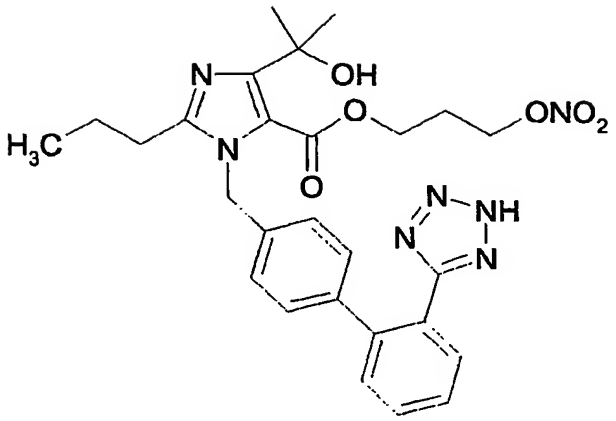
(67)



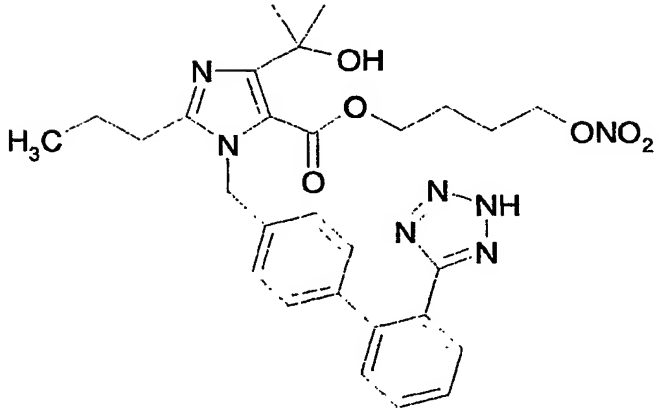
(68)



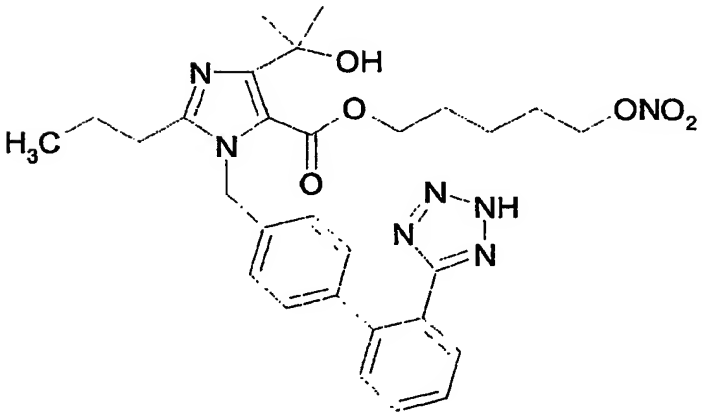
(69)



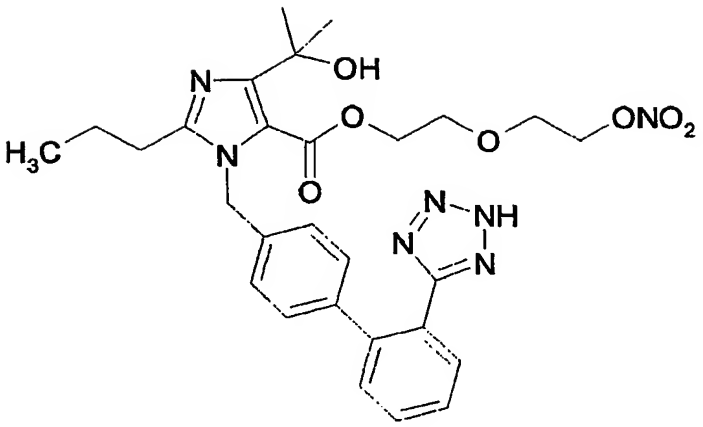
(70)



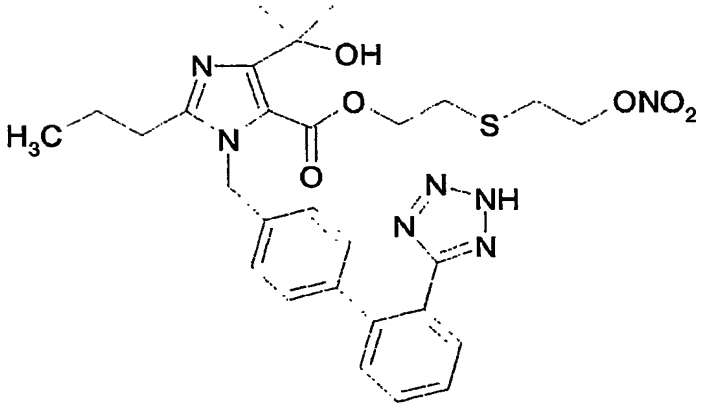
(71)



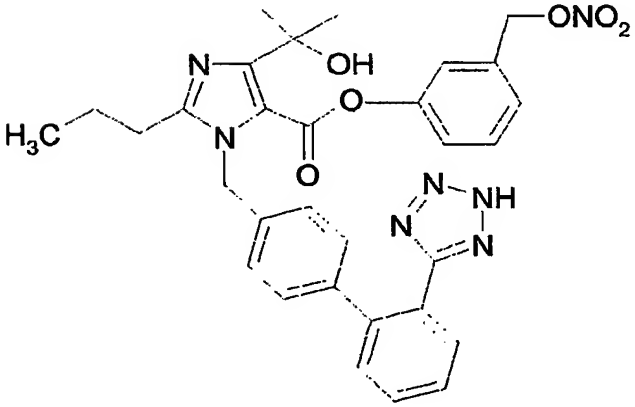
(72)



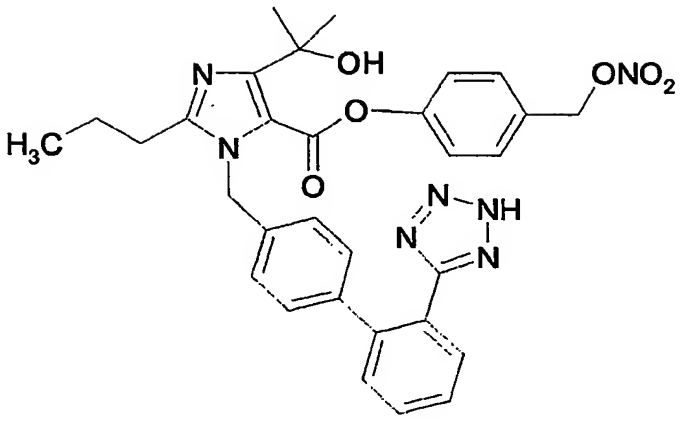
(73)



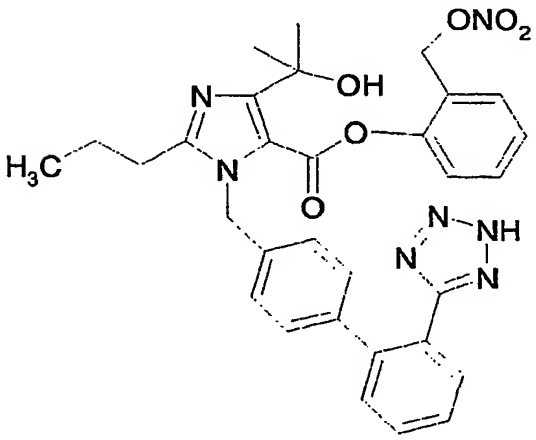
(74)



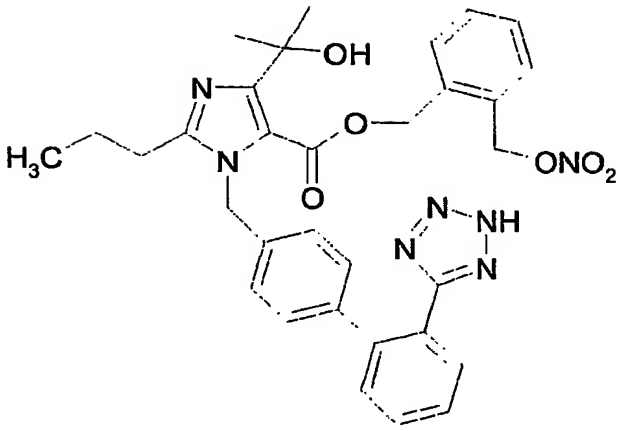
(75)



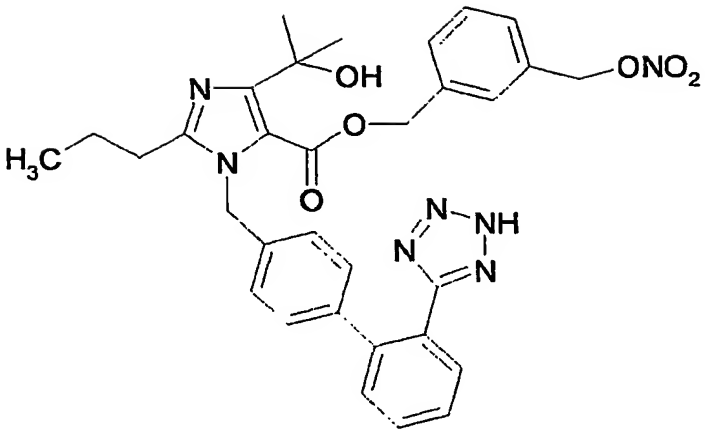
(76)



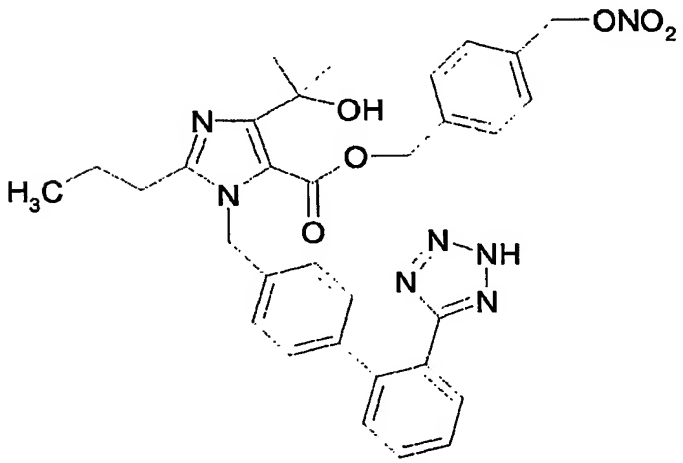
(77)



(78)



(79)



(80)

As mentioned above, object of the present invention are also pharmaceutical compositions containing at least a compound of the present invention of formula (I) together with non toxic adiuvants and/or carriers usually employed in the pharmaceutical field.

The daily dose of active ingredient that should be administered can be a single dose or it can be an effective amount divided into several smaller doses that are to be administered throughout the day. Usually, total daily dose may be in amounts preferably from 50 to 500 mg. The dosage regimen and administration frequency for treating the

mentioned diseases with the compound of the invention and/or with the pharmaceutical compositions of the present invention will be selected in accordance with a variety of factors, including for example age, body weight, sex and medical condition of the patient as well as severity of the disease, route of administration, pharmacological considerations and eventual concomitant therapy with other drugs. In some instances, dosage levels below or above the aforesaid range and/or more frequent may be adequate, and this logically will be within the judgment of the physician and will depend on the disease state.

The compounds of the invention may be administered orally, parenterally, rectally or topically, by inhalation or aerosol, in formulations eventually containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term "parenteral" as used herein, includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Injectable preparations, for example sterile injectable aqueous or oleaginous suspensions may be formulated according to known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents are water, Ringer's solution and isotonic sodium chloride. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono or

diglycerides, in addition fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the active ingredient with a suitable non-irritating excipient, such as cocoa butter and polyethylene glycols.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g. lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavouring and the like.

The compounds of the present invention can be synthesized as follows.

A) The compound of general formula (I) or a pharmaceutically acceptable salt, as above defined:

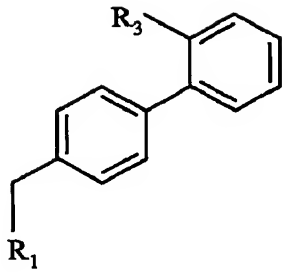
$$R-(Y-ONO_2)_s \qquad (I)$$

when R is the residue of formula (II), can be obtained by a process comprising:

i) reacting a compound of formula (IV):

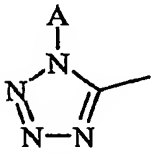
$$R_2-(Y-Hal)_s \qquad (IV)$$

wherein s = 1 and R_2 is the residue of formula (IIA):



(IIA)

wherein R_3 is the group of formula (VA):



(VA)

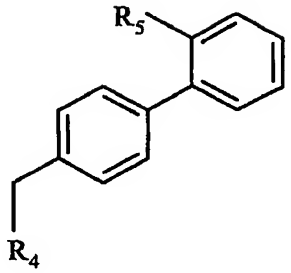
wherein A = H or W, W being a tetrazole protecting group such as trityl, tert-butoxycarbonyl (BOC) and ethyloxycarbonyl or R_3 is -COO-, a group capable to bind Y; R_1 is selected from the groups (IIa)-(IIe), as above defined, wherein N_0 is a group capable to bind Y; Y is as above defined and Hal is an halogen atom preferably Cl, Br or I;

with $AgNO_3$ in a suitable organic solvent such as acetonitrile or tetrahydrofuran (THF) under nitrogen in the dark at temperatures range between 20°-80°C; alternatively the reaction with $AgNO_3$ can be performed under microwave irradiation in solvents such acetonitrile or THF at temperatures in the range between 100-180°C for short time (1-60 min) and

ii) optionally acid hydrolysing the tetrazole protecting group W, as well known in the art, for example as described in T. W. Greene "Protective groups in organic synthesis", Harvard University Press, 1980 and

iii) if desired, converting the resulting compound of general formula (I) into a pharmaceutically acceptable salt thereof.

- The compound of formula (IV) can be obtained by reacting a compound of formula (V):



(V)

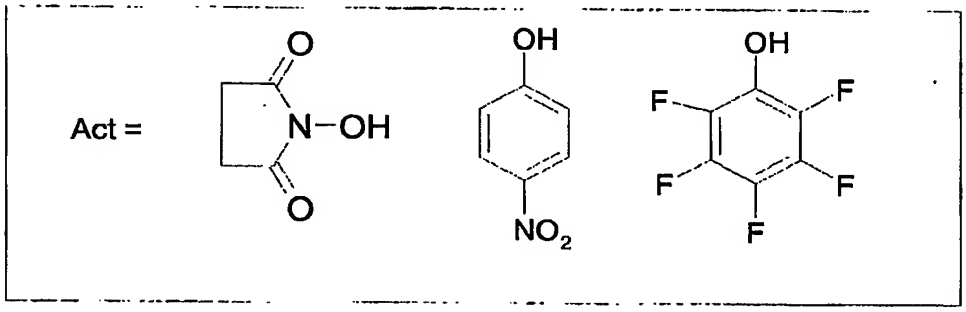
wherein R_5 is the group of formula (VA) as above defined or -COOH and R_4 has the same meaning as R_1 with N_0 = -COOH or -OH,

i.1) when R_5 is the group (VA), $R_4 = R_1$ and R_1 is the group (IIa) wherein m = 1 and N_0 = -OH, with a compound of formula (VI) or (VII):

Hal-Y-COAct (VI)

Hal-Y-OCOAct (VII)

wherein Hal and Y are as above defined and Act is Hal or a carboxylic acid activating group used in peptide chemistry as:



The reaction is generally carried out in presence of a inorganic or organic base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0°-65°C or in a double phase system H_2O/Et_2O at temperatures range between 20°- 40°C;

The compounds of formula (VI) where Act is = Hal are commercially available or can be obtained from the corresponding acids of formula (VIII):

Hal-Y-COOH (VIII)

by well known reactions, for example by reaction with thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert such as toluene, chloroform, DMF, etc. The corresponding acids are commercially available compounds.

The compounds of formula (VI) where Act is not Hal can be obtained from the corresponding compounds of formula (VI) where Act is Hal by reacting with N-Hydroxysuccinimide or with the appropriate substituded phenols in the presence of a base as known in the literature.

The compounds of formula (VII) where Act is = Hal are commercially available or can be obtained from the corresponding alcohols of formula (IX):

Hal-Y-OH (IX)

by reaction with triphosgene in presence of an organic base; the compounds of formula (VII) where Act is not = Hal can be obtained from the corresponding compound (VII) where Act is Hal by reacting with N-Hydroxysuccinimide or with the appropriate substituded phenols in the presence of a base as known in the literature.

Alternatively, the compound of formula (IV) can be obtained by reacting a compound of formula (V) as defined in i.1), with a compound of formula (VIII), as above defined and commercially available, in presence of a condensing agent like dicyclohexylcarbodiimide (DCC), EDAC in the presence of a catalytic amount of DMAP or activating agent as N,N'-carbonyldiimidazole (CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C; i.2) when R_5 is the group (VA) or -COOH, $R_4 = R_1$ and R_1 is selected from the groups (IIa)-(IId) wherein m = 0 and N_0 =

-COOH, with a compound of formula (IX), as above defined, in presence of a condensing agent like dicyclohexylcarbodiimide (DCC), EDAC in the presence of a catalytic amount of DMAP or activating the carboxylic group with agent as N,N'-carbonyldiimidazole(CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C.

The compounds of formula (IX) are commercially available.

Alternatively, transforming the group -COOH into an activated acyl chloride or into another group suitable for esterification, according to methods well known in the literature, and carrying out the esterification in presence of a organic or inorganic base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between 0°-65°C or in a double phase system H_2O/Et_2O at temperatures range between 20°- 40°C;

A1) Alternatively, the compounds of formula (I) as above defined, when R is the residue of formula (II), can be obtained by reacting compounds of formula (V) as above defined:

i.1.1) when R_5 is the group (VA), $R_4 = R_1$ and R_1 is the group (IIa) wherein m = 1 and N_0 = -OH, with a compound of formula (X):

$$O_2NO-Y-COZ \quad (X)$$

where Y is as previously defined and Z is OH or the group Act already defined, with the best suitable synthetical path, for example in presence of a condensing agent like dicyclohexylcarbodiimide (DCC)or EDAC or activating with N,N'-carbonyldiimidazole(CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C and/or in the presence of a organic or inorganic base.

The compounds of formula (X) can be obtained from the corresponding alcohols by reaction with nitric acid and

acetic anhydride in a temperature range from -50°C to 0°C or reacting the corresponding halogen derivatives of formula (VI) or (VIII) with $AgNO_3$ as already described.

i.2.1) when R_5 is the group (VA) or -COOH, $R_4 = R_1$ and R_1 is selected from the groups (IIa)-(IId) wherein m = 0 and N_0 = -COOH, with a compound of formula (XI):

$$O_2NO-Y-OH \quad (XI)$$

wherein Y is as above defined; in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or EDAC or an activating agent as N,N'-carbonyldiimidazole(CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C.

The compound of formula (XI) can be obtained by reacting a compound of formula (IX) with $AgNO_3$ in a suitable organic solvent such as acetonitrile or THF under nitrogen at temperatures range between 20°-80°C;

alternatively the reaction with $AgNO_3$ can be performed under microwave irradiation in solvents such acetonitrile or THF at temperatures in the range between 100-180°C for short time (1-60 min).

Alternatively when R_5 is the group (VA) or -COOH, $R_4 = R_1$ and R_1 is selected from the groups (IIa)-(IIe) wherein m = 0 and N_0 = -COOH, with a compound of formula (XI.1):

$$O_2NO-Y-Hal \quad (XI.1)$$

where Y and Hal are as previously defined by reacting in the presence of an inorganic or organic base able to salify the carboxylic group.

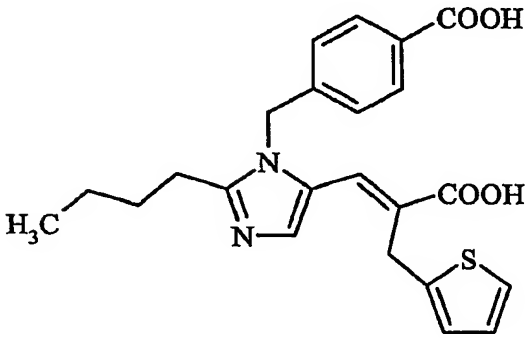
B) The compound of general formula (I), when R is the residue of formula (III), can be obtained by reacting a compound of formula (XII):

$$R_6-(Y-Hal)_s \quad (XII)$$

wherein s = 2, R_6 is the residue (III) and N_1 is -COO-, Y and Hal are as above defined,

with $AgNO_3$ as already described.

Compounds of formula (XII) are obtained by reacting a compound of formula (XIII):



(XIII)

with compounds of formula (IX), as above defined, in presence of a condensing agent like dicyclohexylcarbodiimide (DCC) or EDAC or an activating agent as N,N'-carbonyldiimidazole(CDI) in solvent such as DMF, THF, chloroform at a temperature in the range from -5°C to 50°C as already described.

Alternatively, transforming the group -COOH into an activated acyl chloride or into another group suitable for esterification, according to methods well known in the literature, and carrying out the esterification in presence of a organic or inorganic base in an aprotic polar/non-polar solvent such as THF or CH_2Cl_2 at a temperature in the range between 0°-65°C or in a double phase system.

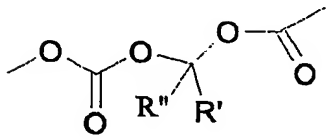
B1) Alternatively, the compounds of general formula (I) as above defined, when R is the residue of formula (III), can be obtained by reacting the compound of formula (XIII) with a compound of formula (XI), as above defined, in presence of a condensing or activating agent as already described.

Alternatively, transforming the group -COOH into a salt with an inorganic or organic base according to methods well known in the literature, and reacting with:

$O_2NO-Y-Hal$ (XI.1)

as known in the literature.

C) The compounds of formula (I), as above defined, when s = 1 and R is the residue of formula (II), wherein R_0 is the tetrazole group and R_1 is the group (IIa) wherein m = 1 and N_0 is



wherein R' and R'' are as above defined,

can be obtained by reacting a compound of formula (IVa):

$R_2-(CR'R''-Hal)_s$ (IVa)

wherein s =1, R_2 and Hal are as above defined, R_3 is the group (VA), R_1 is the group (IIa) wherein m = 1 and N_0 is -OCOO-,

with a compound of formula (X) as above defined, in presence of an organic or inorganic base in a polar solvent as DMF, THF, acetonitrile at a temperature in the range from -5°C to 60°C or in a double phase system as already known in the literature.

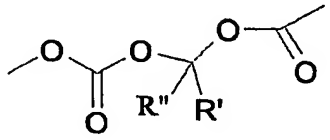
The compounds (IVa) can be obtained by reacting a compound of formula (V) as above defined, wherein R_5 is the group (VA), $R_4 = R_1$ and R_1 is the group (IIa) wherein m = 1 and N_0 = -OH, with a compound of formula (VIIa):

Hal-CR'R''-OCOAct (VIIa)

where Act as the same meaning above described for (VII), in the same manner already described for the compounds (IV); and optionally acid hydrolysing the tetrazole protecting group as above described.

D) The compounds of formula (I), as above defined, when s =1 and R is the residue of formula (II), wherein R_0

is the tetrazole group and R_1 selected from the groups (IIa)-(IIc) wherein m = 0 and N_0 is



wherein R' and R'' are as above defined,

can be obtained by reacting a compound of formula (V), wherein R_5 is the group (VA), $R_4 = R_1$ and R_1 is the group (IIc) wherein N_0 = -COOH, with a compound of formula (XIV):

$$Hal\text{-}CR'R''\text{-}OCOO\text{-}Y\text{-}ONO_2 \quad (XIV)$$

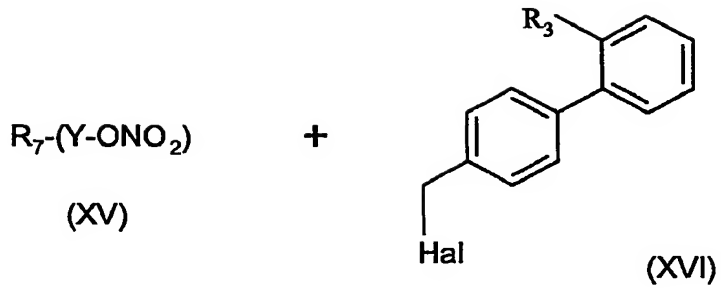
wherein Hal, Y, R' and R'' are as above defined,

in presence of an organic or inorganic base in a polar solvent as DMF, THF, acetonitrile at a temperature in the range from -5°C to 60°C or in a double phase system as already known in the literature.

Compounds of formula (XIV) can be obtained by reacting compounds (XI) with compounds (VIIa) as above defined.

The reaction is generally carried out in presence of a base in an aprotic polar/non-polar solvent such as THF or CH_2Cl_2 at temperatures range between 0°-65°C or in a double phase system H_2O/Et_2O at temperatures range between 20°- 40°C; and optionally acid hydrolysing the tetrazole protecting group as above described.

E) the compounds of formula (I), as above defined, when s = 1 and R is the residue of formula (II), wherein R_0 is the tetrazole group and R_1 is selected from the groups (IIa)-(IIc) can also be obtained reacting compound of formula (XV) with a compound of formula (XVI) commercially available:



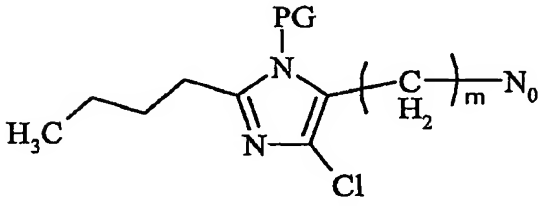
where R_7 is the residue (IIa)-(IIc), R_3 is the group (VA) and Hal is as already defined. The reaction is generally carried out in presence of a base in an aprotic polar/non-polar solvent such as DMF, THF or CH_2Cl_2 at temperatures range between -15°-+80°C or in a double phase system H_2O/Et_2O at temperatures range between 20°- 40°C; and eventually acid hydrolysing the tetrazole protecting group as above described.

Compounds of formula (XV) can be obtained by reacting compounds of formula (XVII):

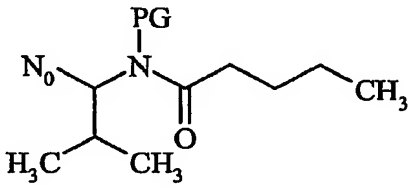
$$R_8-(Y-Hal)$$

(XVII)

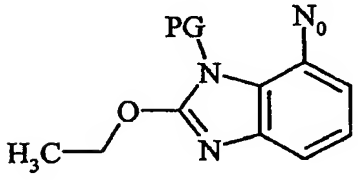
wherein R_8 is the residue of formula (IIa.1), (IIb.1) or (IIc.1):



(IIa.1)



(IIb.1)

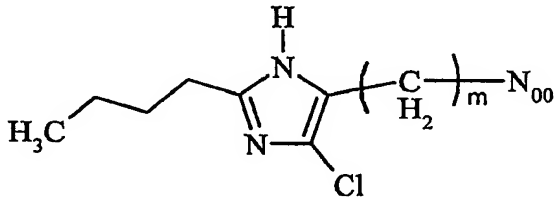


(IIc.1)

wherein PG is a N-protecting group such as BOC or trityl, with $AgNO_3$ as already described and optionally hydrolysing the N-protective group.

Compounds (XVII) where R_8 is (IIa.1) wherein m =1 and N_0 = -OCO- can be obtained from the corresponding alcohols by reaction with a compound of formula (VI) or (VII) as already described.

The alcohols above defined, are obtained by known protection and reduction reactions from commercially available compounds of formula (IIa.2):



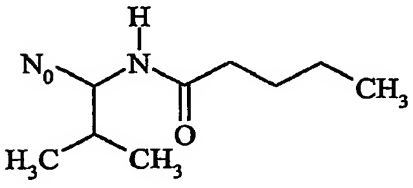
(IIa.2)

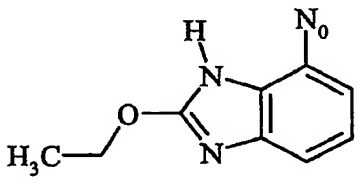
wherein m is 0 and N_{00} is -CHO.

Compounds (XVII) where R_8 is (IIa.1) with m = 0 and N_0 = -COO- or R_8 is (IIb.1) or (IIc.1) with N_0 = -COO- can be obtained from the corresponding acids by reaction with compounds of formula (IX) as already described.

The corresponding acids of (IIa.1) above defined, are obtained from compounds (IIa.2) wherein m is 0 and N_{oo} is -CHO by known protection and oxidation reactions.

The corresponding acids of (IIb.1) and (IIc.1) above defined, are obtained from commercially available (IIb.2) and (IIc.2):





(IIb.2) (IIc.2)

wherein N_0 is -COOH by known protection reations.

The following examples are to further illustrate the invention without limiting it.

Example 1

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl) benzoic acid ester (corresponding to compound (4))

Triphenylmethyl chloride (4.68 g, 16.8 mmol) was added in portions to a solution of Losartan potassium salt (7.0 g; 15.2 mmol) in THF (150 ml). The resulting mixture was stirred at room temperature for 24 hours. Then the reaction was adsorbed on silica gel and purified by flash chromatography (n-Hexane/AcOEt 6:4) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol** (6.7 g, 66%).

From this compound the title compound **(4)** can be achieved through two different synthetic procedure:

Synthetic procedure A

To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol), 4-(nitrooxymethyl)benzoic acid (0.66 g, 3.38 mmol) and *N,N*-dimethylaminopyridine (0.049 g, 0.4 mmol) in CH_2Cl_2 (20 ml) and THF (6 ml) cooled to 0° C, a solution of dicyclohexylcarbodiimide (0.722 g, 3.50 mmol) in CH_2Cl_2 (5 ml) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea

was filtered off, and the organic phase was concentrated. The crude material was purified by silica gel chromatography (n-Hexane/AcOEt 75:25) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester** (1.2 g, 55%) as a white solid.

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester (1.2 g, 1.42 mmol) was dissolved in CH_2Cl_2 (10 ml) and HCl was bubbled into the solution for 20 min. The mixture was the then concentrated and purified by flash chromatography (CH_2Cl_2/Acetone 8:2 then Acetone) affording a crude compound that was dissolved in H_2O/CH_3CN and freeze-dried affording **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester** as a white solid (0.304 g, 36 %).

^{1}H-NMR (DMSO-d_6): 7.73-7.56 (7H,m); 7.24 (1H,d); 7.00(4H,m); 5.60(2H,s); 5.39(2H,s); 5.28(2H,s); 2.61(2H,t); 1.53(2H,m); 1.28(2H,m); 0.82(3H,t).

Synthetic procedure B

To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol), 4-(chloromethyl)benzoic acid (0.571 g, 3.35 mmol) and *N,N*-dimethylaminopyridine (0.049 g, 0.4 mmol) in CH_2Cl_2 (20 ml) and THF (6 ml) cooled to 0 °C, dicyclohexylcarbodiimide (0.644 g, 3.12 mmol) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase

was concentrated. The crude material was purified by flash chromatography (n-Hexane/AcOEt 75:25) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(chloromethyl)benzoic acid ester** (1.56 g, yield 73%).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(chloromethyl)benzoic acid ester (0.807 g, 0.98 mmol) was dissolved in CH_3CN (15 ml) and $AgNO_3$ (0.305 g, 1.8 mmol) was added, in the dark and under nitrogen. The mixture was stirred at 60 °C for 6 hours. Then the precipitated silver salts were filtered off and the organic phase was diluted with ACOEt and washed with NaH_2PO_4 (5%, 2 x 10 ml) and brine (2 x 10 ml), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (n-Hexane/AcOEt 75:25) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester** (0.553 g, 66%).

From 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester the title compound **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-(nitrooxymethyl)benzoic acid ester** was obtained by acid hydrolysis as described in Procedure A.

Example 2

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester (corresponding to compound (2))

This compound can be achieved through four different synthetic procedure:

Synthetic procedure A

To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol) (obtained in Example 1), 4-nitrooxybutanoic acid (0.536 g, 3.6 mmol) and *N,N*-dimethylaminopyridine (0.05 g, 0.4 mmol) in CH_2Cl_2 (20 ml) and THF (6 ml) cooled to 0° C, a solution of dicyclohexylcarbodiimide (DCC) (0.722 g, 3.50 mmol) in CH_2Cl_2 (5 ml) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase was concentrated. The crude material was purified by flash chromatography (n-Hexane/EtOAc 7:3) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester** (1.45 g, 70%).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester (1.0 g, 1.25 mmol) was dissolved in CH_2Cl_2 (20 ml) and HCl was bubbled into the solution for 20 min. The reaction was then concentrated and purified by flash chromatography (CH_2Cl_2/ Acetone 8:2 then Acetone) affording crude compound as a white foam. That was dissolved in H_2O/CH_3CN and freeze dried to give **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester** (0.507 g, yield 71%)as a white solid.

^{1}H-NMR (DMSO-d_6): 7.66 (2H,d); 7.57 (1H,d); 7.49 (1H,d); 7.09 (2H,d); 6.95 (2H,d); 5.25 (2H,s); 4.99 (2H,s); 4.49

(2H,t); 2.54 (2H,t); 2.01 (2H,t); 1.60 (2H,m); 1.49 (2H,m); 1.32 (4H,m); 0.84 (3H,t).

Synthetic procedure B

To a solution of 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (obtained in Example 1) (1.7 g, 2.6 mmol), 4-bromobutanoic acid (0.561 g, 3.36 mmol) and N,N-dimethylaminopyridine (0.05 g, 0.4 mmol) in CH2Cl2 (20 ml) and THF (6 ml) cooled to 0° C, a solution of dicyclohexylcarbodiimide (0.722 g, 3.50 mmol) in CH2Cl2 (5 ml) was slowly added and the reaction was stirred at room temperature for 24 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase was concentrated. The crude material was purified by silica gel chromatography (n-Hexane/ETOAc 75: 25) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromobutanoic acid ester** (1.27 g, yield 60%).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromobutanoic acid ester (1.2 g, 1.47 mmol) was dissolved in CH3CN (20 ml) and AgNO3 (0.475 g, 2.8 mmol) was added in the dark and under nitrogen. The mixture was stirred at 60° C for 8 hours. Then it was partitioned between EtOAc and phosphate buffer (pH=3, 40 ml). The organic phase was washed with phosphate buffer (pH=3, 2 x 25 ml), brine, (3 x 25 ml), dried over Na2SO4 and concentrated. The crude material was purified by flash chromatography (n-Hexane/AcOEt 7:3) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-**

1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester (0.819 g, yield 70%) as a foam.

From 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester the title compound **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester** was obtained by acid hydrolysis as described in Example 2, Procedure A (0.507 g, 71 %).

Synthetic procedure C

To a solution of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (3.6 g, 8.5 mmol), *N,N*-dimethylaminopyridine (0.1 g, 0.85 mmol) and TEA (1.18 ml, 0.85 mmol) in THF (60 ml) cooled to 0 °C and under nitrogen a solution of 4-bromobutanoyl chloride (0.98 ml, 8.5 mmol) in THF (1 ml) was slowly added and the reaction was stirred at room temperature for 1.5 hours. Then it was partitioned between EtOAc and phosphate buffer (pH=3, 40 ml) and extracted with EtOAc (3 x 15 ml). The organic phase was dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (CH_2Cl_2/Acetone 8:2) affording **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromobutanoic acid ester** (2.5 g, yield 51%) as a white solid.

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 4-bromobutanoic acid ester (0.56 g, 0.98 mmol) was dissolved in CH_3CN (15 ml) and $AgNO_3$ (0.83 g, 4.9 mmol) was added in the dark and under nitrogen. The mixture was stirred at 60° C for 8

hours. Then it was cooled and poured into a phosphate buffer solution (pH=3, 40 ml). NaCl solid was added and the mixture was extracted with EtOAc. The organic phase was washed with phosphate buffer (pH=3, 2 x 25 ml), brine, (3 x 25 ml), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (CH2Cl2/acetone 8:2 then acetone) affording crude compound as a white foam. That was dissolved in H_2O/CH_3CN and freeze dried to give **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-1H-imidazole-5-methanol 4-nitrooxybutanoic acid ester** (0.3 g, yield 55%) as a white solid.

Synthetic procedure D

To a solution of 4-bromobutyric acid (0.91 g, 5.4 mmol), pentafluorophenol (1.00 g, 5.4 mmol) and DMAP (0.13 g, 1.1 mmol) in CH_2Cl_2 (10 ml) cooled to 0 °C under nitrogen, N,N-dicyclohexylcarbodiimide (1.70 g, 8.1 mmol) was added in portions. After 1 h the reaction was slowly warmed to room temperature and stirred for 5 hours. The diciclohexylurea was filtered off and the mother liquor was concentrated and purified by flash chromatography (n-Hexane/EtOAc 98:2) affording **4-bromobutyric acid pentafluorophenyl ester** as a colourless oil (1.40 g, 78%).

A mixture of 4-bromobutyric acid pentafluorophenyl ester (0.65 g, 1.9 mmol) and $AgNO_3$ (0.83 g, 4.9 mmol) in CH_3CN (8 ml) was warmed at 70 °C for 20 minutes at the microwave. The formed salts were filtered off, the solvent was concentrated and the residue purified by flash chromatography (n-Hexane/EtOAc 95:5) affording **4-nitrooxybutyric acid pentafluorophenyl ester** as a clear oil (0.38 g, 62 %).

To a solution of 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (0.48 g, 1.1 mmol), TEA (0.16 ml, 1.1 mmol) and DMAP (0.14 mg, 1.1 mmol) in DMF (3 ml), cooled to 0 °C, a solution of 4-nitrooxybutyric acid pentafluorophenyl ester (0.36 g, 1.1 mmol) in DMF (3 ml) was added. The reaction was slowly warmed to room temperature and stirred for 3 hours. Then the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (10 ml) and washed with a buffer solution (pH=3) then with brine. The organic layer was dried over Na_2SO_4, concentrated and purified by flash chromatography (CH_2Cl_2/ MeOH 98:2) to afford the title compound (0.41 g, 66%).

Example 3

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 11-nitrooxyundecanoic acid ester (corresponding to compound (68))

Using The procedure **A** described in **Example 2** but starting from 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (1.7 g, 2.6 mmol) and 11-nitrooxyundecanoic acid (0.78 g, 3.36 mmol), **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 11-nitrooxyundecanoic acid ester** (1.65 g, 80%) was obtained.

From acid hydrolysis of this compound (1.6 g, 2.0 mmol) **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 11-nitrooxyundecanoic acid ester** (0.91 g,70%) was obtained after crystallization from Et_2O/n-Hexane.

(DMSO): 7.66(2H,d); 7.57(1H,d); 7.59(1H,d); 7.09(2H,d); 6.95(2H,d); 5.25(2H,s); 4.99(2H,s); 4.49(2H,t);2.54(2H,t); 2.01(2H,t); 1.62(2H,m); 1.49(2H,m); 1.35-1.14(16H,m); 0.84(3H,t).

Example 4

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 3-(nitrooxymethyl) benzoic acid ester (corresponding to compound (5))

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (Prapared in Example 1) (1.0 g, 1.5 mmol), triethylamine (0.42 ml, 3.0 mmol) and *N,N*-dimethylaminopyridine (36 mg, 0.30 mmol) were dissolved in CH_2Cl_2 (10 ml). Then 3-(chloromethyl)benzoyl chloride (0.24 ml, 1.7 mmol) was added and the reaction was stirred at room temperature for 4 hours. The mixture was diluted with EtOAC (50 ml) and the organic phase was washed with NaH_2PO_4 (5 %, 2 x 25 ml), $NaHCO_3$ (5 %, 2 x 25 ml), brine (2 x 25 ml), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (n-Hexane/EtOAC 75:25) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 3-(chloromethyl)benzoic acid ester** (1.0 g, 81 %) as an oil.

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 3-

(chloromethyl)benzoic acid ester (0.66 g, 0.20 mmol) was suspended in CH_3CN (10 ml) and NaI (0.24 g, 1.6 mmol) was added. The reaction was refluxed for 1 hour, then diluted with EtOAc (25 ml). The organic phase was washed with H_2O (3 x 25 ml), dried over $NaSO_4$ and concentrated. The crude material was dissolved in CH_3CN (4 ml) and $AgNO_3$ (0.34 g, 2 mmol) was added in the dark and under nitrogen. The reaction was stirred at room temperature for 2 hours, then it was diluted with EtOAC (10 ml). The organic phase was washed with NaH_2PO_4 (5 %, 2 x 10 ml) and brine (2 x 10 ml), dried over $NaSO_4$ and concentrated. The crude material was purified by flash chromatography (Hexane/EtOAc 75:25), affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 3-(nitrooxymethyl)benzoic acid ester** (230 mg, 33 %).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 3-(nitrooxymethyl)benzoic acid ester (0.23 g, 0.27 mmol) was dissolved in CH_2Cl_2 (5 ml) and HCl was bubbled in the solution. 10 minutes later the reaction was concentrated and purified by flash chromatography (CH_2Cl_2/acetone 8:2 and then acetone). The yellow foam obtained was treated over decolorizing carbon, dissolved in H_2O/CH_3CN and

freeze-dried affording **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol m-nitrobenzylbenzoic acid ester** as a white solid (0.11 g, 63 %).

($CDCl_3$): 7.90 (2H,m); 7.78 (1H,d); 7.56 (3H,m); 7.40 (1H,m); 7.19 (1H,d); 7.06 (2H,d); 6.83 (2H,d); 5.40 (2H,s); 5.24 (2H,s); 5.14 (2H,s); 2.47 (2H,t); 1.61 (2H,m); 1.32 (2H,m); 0.87 (3H,m).

Example 5

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-nitrooxyhexanoic acid ester (corresponding to compound (69)

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol (prepared in **Example 1**) (2.0 g, 3.0 mmol), 6-bromohexanoic acid (0.90 g, 4.6 mmol), *N,N*-dimethylaminopyridine (38 mg, 0.3 mmol), triethylamine (1.3 ml, 9.3 mmol) were dissolved in CH_2Cl_2 (20 ml) and the solution was cooled to 0°C. Then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) (0.94 g, 9.3 mmol) was added and the reaction was slowly warmed to room temperature and stirred overnight. The organic phase was washed with NaH_2PO_4 (5 %, 20 ml) and brine (20 ml), dried over Na_2SO_4 and purified by flash chromatography (n-Hexane/EtOAc 7:3) affording **2-butyl-4-**

chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-bromohexanoic acid ester as an oil (1.94 g, 76 %).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-bromohexanoic acid ester (0.77 g, 0.90 mmol) and NaI (0.30 g, 2.0 mmol) were dissolved in CH_3CN (10 ml) and the mixture was refluxed for 1 hour. Then it was diluted with EtOAc (50 ml) and the organic phase was washed with H_2O (2 x 25 ml), dried over Na_2SO_4 and concentrated. The crude was suspended in CH_3CN (7 ml) and $AgNO_3$ (0.60 g, 3.5 mmol) was added. The reaction was stirred at room temperature, in the dark and under nitrogen, for 3 hours. Then it was partitioned between EtOAc (30 ml) and phosphate buffer (pH=3, 25 ml). The organic phase was washed with phosphate buffer (pH=3, 2 x 25 ml) and brine (3 x 25 ml), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (n-Hexane/EtOAc 7:3) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-nitrooxyhexanoic acid ester** as a foam (0.69 g, 64 %).

2-butyl-4-chloro-1-[[2'-(1-triphenylmethyl-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-nitrooxyhexanoic acid ester (0.88 g) was dissolved in

CH_2Cl_2 (20 ml) and HCl was bubbled into the solution for 20 minutes. The mixture was then concentrated and purified by flash chromatography (CH_2Cl_2/acetone 8:2 and then acetone) affording the product as a yellow foam. That was treated with decolorizing carbon, dissolved in H_2O/CH_3CN and freeze-dried to give product **2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol 6-nitrooxyhexanoic acid ester** as a white solid (0.41 g, 68 %).

($CDCl_3$): 7.79 (1H, d); 7.63-7.49 (2H, m); 7.41 (1H, d); 7.08 (2H, d); 6.77 (2H, d); 5.14 (2H, s); 4.88 (2H, s); 4.38 (2H, t); 2.38 (2H, t); 2.06 (2H, m); 1.70-1.50 (6H, m); 1.37-1.30 (4H, m); 0.85 (3H, t).

Example 6

2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid (3-nitrooxy)propyl ester (corresponding to compound (7))

To a solution of 2-butyl-4-chloro-5-formyl imidazole (1.2 g, 6.4 mmol) in t-ButOH (35 ml) and 5% aqueous Na_2HPO_4 solution (25 ml), a solution of $KMnO_4$ (6.1 g, 38.6 mmol) in water (40 ml) was added. After 6 minutes at room temperature, the mixture was quenched by addition of 40% aqueous $NaHSO_3$ solution. The suspension was filtered, washed with H_2O and the filtrate was freeze-dried. The residue was taken up with H_2O (50 ml) acidified to pH 2.5 with HCl 3N and extracted with EtOAc (3 ×70 ml). The combined organic extracts were dried over Na_2SO_4 and

evaporated to dryness to give **2-butyl-4-chloro-imidazole 5-carboxylic acid** (1.07 g, 83%) as a white solid.

To a solution of 2-butyl-4-chloro-imidazole 5-carboxylic acid (0.61 g, 3 mmol), 3-bromopropanol (0.52 g, 3.74 mmol) and *N,N*-dimethylaminopyridine (0.08 g, 0.65 mmol) in THF (12 ml) cooled to 0° C, dicyclohexylcarbodiimide (0.91 g, 4.4 mmol) was slowly added in portions and the reaction was stirred at room temperature for 4 hours. Then the formed dicyclohexylurea was filtered off, and the organic phase was concentrated. The crude material was purified by silica gel chromatography (n-Hexane/AcOEt 8:2) affording **2-butyl-4-chloro-imidazole 5-carboxylic acid 3-bromopropyl ester** (0.5 g, 50%) as a white foam.

2-butyl-4-chloro-imidazole 5-carboxylic acid 3-bromopropyl ester (0.807 g, 2.47 mmol) was dissolved in CH_3CN (15 ml) and $AgNO_3$ (0.63 g, 3.7 mmol) was added. The mixture was stirred at room temperature for 8 h. Then the precipitated silver salts were filtered off and the organic phase was diluted with ACOEt and washed with NaH_2PO_4 (5%, 2 x 10 ml) and brine (2 x 10 ml), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (n-Hexane/AcOEt 70:30) affording **2-butyl-4-chloro-imidazole 5-carboxylic acid 3-nitrooxypropyl ester** (0.377 g, 50%).

To a solution of 2-butyl-4-chloro-imidazole 5-carboxylic acid 3-nitrooxypropyl ester (0.76 g, 2.5 mmol) in dimethylacetamide (DMA) (13 ml) cooled to 0 °C and under nitrogen, potassium *tert*-butylate (0.28 g, 2.5 mmol) was slowly added in portions. After 10 min stirring a solution of N-(triphenylmethyl)-5-(4'-bromomethylbiphenyl-2-yl-)tetrazole (1.7 g, 3 mmol) in DMA (10 ml) was added and the

mixture was stirred at room temperature for 1 h. Then the mixture was partitioned between water and EtOAc. The organic phase was separated, dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (n-Hexane/EtOAc 7:3) affording **2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid 3-nitrooxypropyl ester** (1.56 g, 80%).

From 2-butyl-4-chloro-1-[[2'-(1-triphenylmethyltetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole-5-carboxylic acid 3-nitrooxypropyl ester (1 g, 1.28 mmol) the title compound (white solid) was achieved through acid hydrolysis as described for analogous compound in **Example 1** procedure A (0.28 g, 40%).

^{1}H-NMR (DMSO-d_6): 7.60-7.20 (4H,m); 7.12 (2H,d); 6.92 (2H,d); 5.72 (2H,s); 4.58 (2H,t); 4.50 (2H,t); 2.54 (2H,t); 2.31 (2H,m); 1.49 (2H,m); 1.32 (2H,m); 0.84 (3H,t).

Studies on vascular tone

The ability of the nitroderivatives of ARB to induce vasorelaxation in comparison to native ARB, was tested *in vitro* in isolated rabbit thoracic aorta preparations (Wanstall J.C. et al., Br. J. Pharmacol., 134:463-472, 2001). Male New Zealand rabbits were anaesthetized with thiopental-Na (50 mg/kg, iv), sacrificed by exsanguinations and then the thorax was opened and the aorta dissected. Aortic ring preparations (4 mm in length) were set up in physiological salt solution (PSS) at 37°C in small organ chambers (5 ml). The composition of PSS was (mM): NaCl 130, $NaHCO_3$ 14.9, KH_2PO_4 1.2, $MgSO_4$ 1.2, HEPES 10, $CaCl_2$, ascorbic acid 170 and glucose 1.1 (95% O_2 /5% CO_2 ; pH 7.4). Each ring was mounted under 2 g passive tension. Isometric tension was recorded with a Grass transducer (Grass FT03)

attached to a BIOPAC MP150 System. Preparations were allowed to equilibrate for 1h, and then contracted submaximally with noradrenaline (NA, 1 μM) and, when the contraction was stable, acetylcholine (ACh, 10 μM) was added. A relaxant response to ACh indicated the presence of a functional endothelium. Vessels that were unable to contract NA or showed no relaxation to Ach were discarded. When a stable precontraction was reached, a cumulative concentration-response curve to either of the vasorelaxant agents was obtained in the presence of a functional endothelium. Each arterial ring was exposed to only one combination of inhibitor and vasorelaxant. Moreover, the effect of the soluble guanylyl cyclase inhibitor ODQ (1-H-(1,2,4)-oxadiazol(4,3-a)quinoxalin-1-one) on vasorelaxation elicited by the compounds was examined preincubating the aortic rings with ODQ (10 μM) for 20 min.

Responses to relaxing agents are expressed as a percentage of residual contraction and plotted against concentration of test compound. IC_{50} values (where IC_{50} is the concentration producing 50% of the maximum relaxation to the test compound) were interpolated from these plots.

During the experimental period, the plateau obtained with NA was stable without significant spontaneous loss of contraction in the aortic rings. Under these experimental conditions, the ARB losartan, did not produce relaxation at any of the concentration tested, the curve being not different from that built up in the presence of vehicle alone.

As shown in Table 1, the nitroderivatives of the invention were able to induce relaxation in a concentration-dependent manner. Furthermore, in experiments performed in the presence of ODQ (10 μM), the vasorelaxant responses to tested compounds were inhibited.

Table 1

Compound	**IC_{50} (μM)** ± sem
Losartan	no effect up to 100 μM
Compound of **EX.1**	33 ± 12
Compound of **EX.2**	15 ± 3
Compound of **EX.4**	54 ± 16
Compound of **EX.5**	18 ± 6

IC_{50} is the concentration which inhibits 50% of the response.

Effect of losartan nitroderivative on inflammatory pathways *in vitro*

The experiments were performed using RAW 264.7 monocyte macrophage cell line. Cells were stimulated in the presence of lipopolysaccharide (LPS) (1 μg/ml) for 16 hrs. At the end of the incubation, the culture media were collected and analyzed for nitrite content using a standard Griess reaction.

The results reported in Table 2 are expressed as % of nitrite content for each treatment vs. LPS-treated samples.

Table 2

Study of inhibition of LPS-induced nitrite accumulation in RAW 264.7 macrophages		
Compound	**Concentration (μM)**	**Nitrite (% *vs* vehicle)**
Losartan	25	99± 9
Compound of **EX.4**	25	61± 3

As shown in Table 2, differently from the parent compound, the nitroderivative (compound of Ex.4) was able to inhibit the accumulation of nitrites induced by LPS.

Study of antiplatelet activity of losartan nitroderivatives *in vitro*

The ability of losartan nitroderivatives to inhibit platelet aggregation was evaluated *in vitro* in human platelets. Platelet aggregation was measured in 0.25 ml platelet reach plasma (PRP) samples according to Born method (Gresele P, Arnout J, Deckmyn H, *et al.*, J Clin Invest. 1987;80:1435-45). Aggregating agent used was U46619, a TxA_2 analog, based on the evidence that this agonist is sensitive to the effects of nitric oxide. Compounds were incubated at 37°C for 2 min before adding the aggregating agent. Aggregation was followed for 5 min and the maximal amplitude (cm) was measured. DMSO (0.05% final concentration) was used as vehicle. Compounds were tested at concentrations ranging from 10 to 100μM.

Table 3

Study of antiplatelet activity of losartan nitroderivatives *vs* losartan in human platelets	
Compound	**Platelet aggregation (PRP)** (incubation time: 2 min) IC_{50} μM
Losartan	33
Compound of **EX.1**	5
Compound of **EX.2**	11

As shown in Table 3, the nitroderivatives were able to significantly inhibit platelet aggregation induced by U46619. Losartan showed a weak effect.

Study of antihypertensive activity of losartan nitroderivative *in vivo*

The ability of losartan nitroderivative (compound of Ex.2) to decrease blood pressure was evaluated in conscious spontaneously hypertensive rats (SHRs). Two groups of SHRs (250-300 g) received a daily oral dose of either losartan (10 mg/kg po) or losartan nitroderivative (equimolar dose) for 3 days. Systolic blood pressure (SBP) and heart rate were monitored by telemetry at different time points after dosing.

Table 4

Systolic blood pressure (mmHg)				
Compound	**Baseline**	**30 min**	**12 hrs**	**24 hrs**
Losartan (10 mg/kg po)	143	133	135	136
Compound of **EX.2** (12 mg/kg po)	143	115	126	128

As shown in Table 4, differently from the parent compound, the nitroderivative (compound of Ex.2) was able to induce a clear reduction in blood pressure levels over the treatment period.